

VU Research Portal

Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits

Boomsma, Dorret I.; de Geus, Eco J.C.; Hottenga, Jouke Jan; Willemsen, Gonneke; the Million Veteran Program

published in

Nature Genetics
2018

DOI (link to publisher)

[10.1038/s41588-018-0205-x](https://doi.org/10.1038/s41588-018-0205-x)

document version

Publisher's PDF, also known as Version of record

document license

Article 25fa Dutch Copyright Act

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Boomsma, D. I., de Geus, E. J. C., Hottenga, J. J., Willemsen, G., & the Million Veteran Program (2018). Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nature Genetics*, 50(10), 1412-1431. <https://doi.org/10.1038/s41588-018-0205-x>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Corrected: Publisher Correction

Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits

High blood pressure is a highly heritable and modifiable risk factor for cardiovascular disease. We report the largest genetic association study of blood pressure traits (systolic, diastolic and pulse pressure) to date in over 1 million people of European ancestry. We identify 535 novel blood pressure loci that not only offer new biological insights into blood pressure regulation but also highlight shared genetic architecture between blood pressure and lifestyle exposures. Our findings identify new biological pathways for blood pressure regulation with potential for improved cardiovascular disease prevention in the future.

High blood pressure is a leading heritable risk factor for stroke and coronary artery disease, responsible for an estimated 7.8 million deaths and 148 million disability life years lost worldwide in 2015 alone¹. Blood pressure is determined by complex interactions between life-course exposures and genetic background^{2–4}. Previous genetic association studies have identified and validated variants at 274 loci with modest effects on population blood pressure, explaining in aggregate ~3% of the trait variance^{5–12}.

Here we report genome-wide discovery analyses of blood pressure traits—systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP)—in people of European ancestry drawn from UK Biobank (UKB)¹³ and the International Consortium of Blood Pressure Genome Wide Association Studies (ICBP)^{11,12}. We adopted a combination of a one- and two-stage study design to test common and low-frequency single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) $\geq 1\%$ associated with blood pressure traits (Fig. 1). In all, we studied over 1 million people of European descent, including replication data from the US Million Veteran Program (MVP, $n = 220,520$)¹⁴ and the Estonian Genome Centre, University of Tartu (EGCUT, $n = 28,742$) Biobank¹⁵.

UKB is a prospective cohort study of ~500,000 richly phenotyped individuals, including blood pressure measurements¹³, with genotyping by customized array and imputation from the Haplotype Reference Consortium (HRC) panel, yielding ~7 million SNPs (imputation quality score (INFO) ≥ 0.1 and MAF $\geq 1\%$)¹⁶. We performed genome-wide association studies (GWAS) of blood pressure traits ($n = 458,577$ Europeans) under an additive genetic model¹⁷ (Supplementary Table 1a). Following linkage disequilibrium (LD) score regression¹⁸, genomic control was applied to the UKB data before meta-analysis (Methods).

In addition, we performed GWAS analyses for blood pressure traits in newly extended ICBP GWAS data comprising 77 independent studies of up to 299,024 Europeans genotyped with various arrays and imputed to either the 1000 Genomes Reference Panel or the HRC platforms (Supplementary Table 1b). After quality control, we applied genomic control at the individual study level and obtained summary effect sizes for ~7 million SNPs with INFO ≥ 0.3 and heterogeneity Cochran's Q statistic¹⁹ filtered at $P \geq 1 \times 10^{-4}$ (Methods). We then combined the UKB and ICBP GWAS results using inverse-variance-weighted fixed-effects meta-analysis (Methods), giving a total discovery sample of up to 757,601 individuals²⁰.

In our two-stage design, we attempted replication (in MVP and EGCUT; Supplementary Table 1c) of 1,062 SNPs at $P < 1 \times 10^{-6}$ from discovery with concordant effect direction between UKB and ICBP, using the sentinel SNP (that is, the SNP with smallest P -value

at the locus) after excluding the HLA region (chr. 6: 25–34 MB) and all SNPs in LD ($r^2 \geq 0.1$) or ± 500 kb from any previously validated blood pressure-associated SNPs at the 274 published loci. Our replication criteria were genome-wide significance ($P < 5 \times 10^{-8}$) in the combined meta-analysis, $P < 0.01$ in the replication data, and concordant direction of effect between discovery and replication.

We also undertook a one-stage design to reduce type II error from the two-stage analysis. We used $P < 5 \times 10^{-9}$ as threshold from the discovery meta-analysis—that is, an order of magnitude more stringent than genome-wide significance²¹—and required an internal replication $P < 0.01$ in each of the UKB and ICBP GWAS analyses, with concordant direction of effect, to minimize false positive findings.

We carried out conditional analyses using GCTA, a tool for genome-wide complex trait analysis²². We then explored putative functions of blood pressure-associated signals using a range of in silico resources and evaluated co-occurrence of blood pressure-associated loci with lifestyle exposures and other complex traits and diseases. Finally, we developed a genetic risk score (GRS) and assessed impact of blood pressure-associated variants on blood pressure, risk of hypertension and other cardiovascular diseases and in other ethnicities.

Results

We present a total of 535 novel loci (Fig. 2 and Supplementary Fig. 1): 325 claimed from the two-stage design (Supplementary Tables 2a–c) and an additional 210 claimed from our one-stage design with internal replication (Supplementary Tables 3a–c). Our two-stage design uniquely identified 121 variants, while 204 also met the one-stage criteria (Fig. 3a); many loci would not have been detected by either the one- or two-stage designs alone (Fig. 3a). For SBP, the distributions of effect sizes are similar for the one-stage (median = 0.219 mm Hg per allele; inter-quartile range (IQR) = 0.202–0.278) and two-stage loci (median = 0.224; IQR = 0.195–0.267) ($P = 0.447$) (Supplementary Fig. 2). Of the 210 loci found only in the one-stage analysis, 186 were also genome-wide significant ($P < 5 \times 10^{-8}$) in the combined meta-analysis, with all variants except 1 having concordant direction of effect between discovery and replication (Supplementary Tables 3a–c); of the remaining 24 SNPs, 10 still had concordant direction of effect.

We find support in our data for all 274 previously published blood pressure loci (Supplementary Figs. 1 and 2 and Supplementary Table 4); >95% of the previously reported SNPs covered within our data are genome-wide significant. Only 6 available SNPs did not reach Bonferroni significance, likely because they were originally

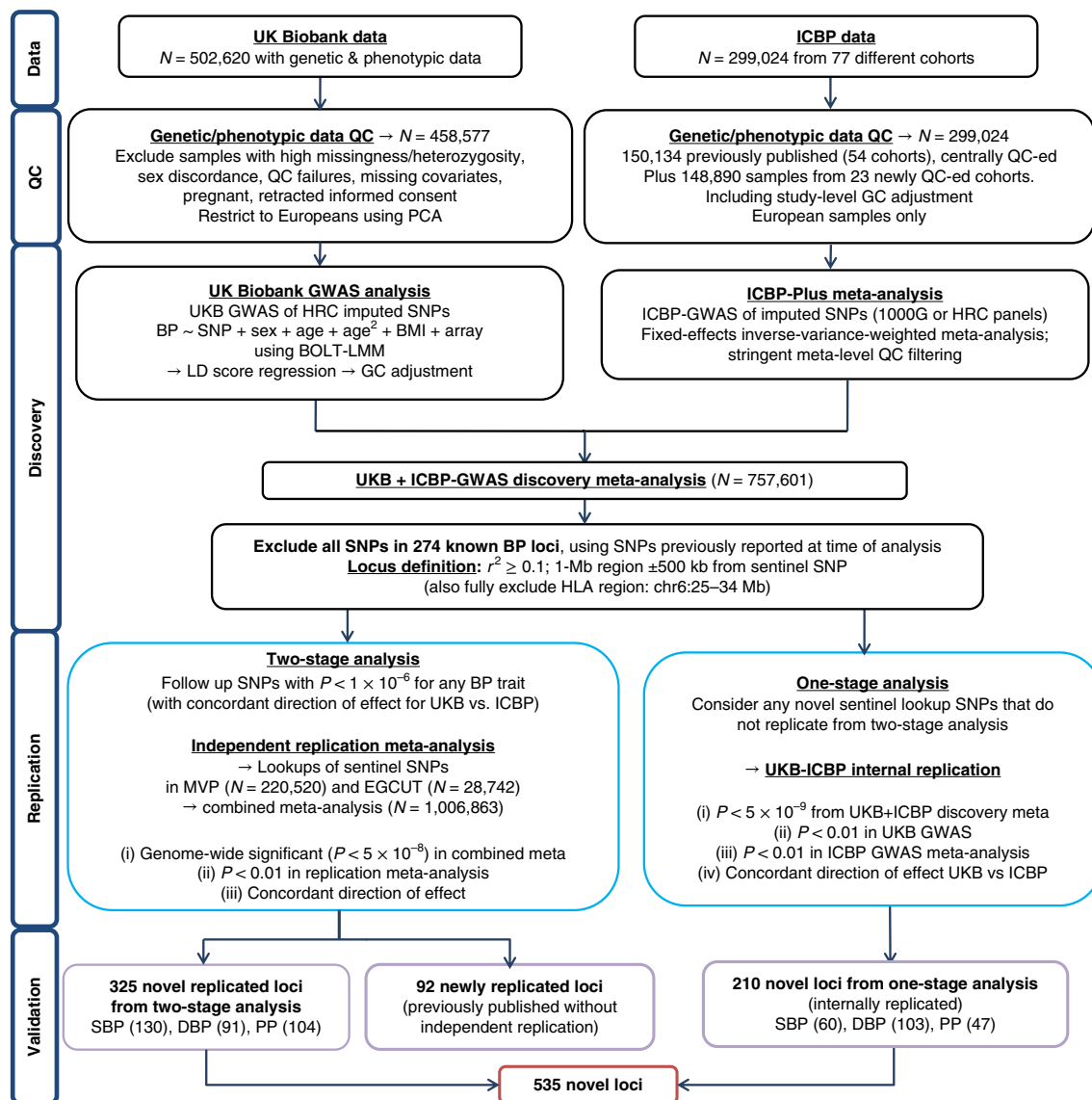


Fig. 1 | Study design schematic for discovery and validation of loci. ICBP; International Consortium for Blood Pressure; N, sample size; QC, quality control; GC, genomic control; PCA, principal component analysis; GWAS, genome-wide association study; 1000G, 1000 Genomes; HRC, Haplotype Reference Consortium panel; LMM, linear mixed model; UKB, UK Biobank; MAF, minor allele frequency; HLA, human leukocyte antigen; MVP, Million Veteran Program; EGCUT, Estonian Genome Center, University of Tartu.

identified in non-European ancestries (for example, rs6749447, rs10474346, rs11564022) or from a gene–age interaction analysis (rs16833934). In addition, we confirmed a further 92 previously reported but not replicated loci (Supplementary Table 5)⁹; together with 274 previously reported loci confirmed and 535 novel loci identified here, there are 901 blood pressure–associated loci in total.

Novel genetic loci for blood pressure. Of the 535 independent novel loci, 363 SNPs were associated with one blood pressure trait, 160 with two traits and 12 with all three (Fig. 3b and Supplementary Fig. 3). Using genome-wide complex trait conditional analysis, we further identified 163, genome-wide significant, independent secondary signals with $MAF \geq 1\%$ associated with blood pressure (Supplementary Table 6), of which 19 SNPs were in LD ($r^2 \geq 0.1$) with previously reported secondary signals. This gives a total of 144 new secondary signals; hence, we now report over 1,000 independent blood pressure signals.

The estimated SNP-wide heritability (h^2) of blood pressure traits in our data was 0.213, 0.212 and 0.194 for SBP, DBP and PP,

respectively, with a gain in percentage of blood pressure variance explained. For example, for SBP, percentage variance explained increased from 2.8% for the 274 previously published loci to 5.7% for SNPs identified at all 901 loci (Supplementary Table 7).

Functional analyses. Our functional analysis approach is summarized in Supplementary Fig. 4. First, for each of the 901 loci, we annotated all SNPs (based on LD $r^2 \geq 0.8$) to the nearest gene within 5 kb of a SNP, identifying 1,333 genes for novel loci and 1,272 genes for known loci. Then we investigated these loci for tissue enrichment, DNase hypersensitivity site enrichment and pathway. At 66 of the 535 novel loci, we identified 97 non-synonymous SNPs, including 8 predicted to be damaging (Supplementary Table 8).

We used chromatin interaction Hi-C data from endothelial cells (HUVEC)²³, neural progenitor cells (NPC), mesenchymal stem cells (HVMSC) and tissue from the aorta (HAEC) and adrenal gland²⁴ to identify distal associated genes. There were 498 novel loci that contained a potential regulatory SNP, and in 484 of these we identified long-range interactions in at least one of the tissues or cell

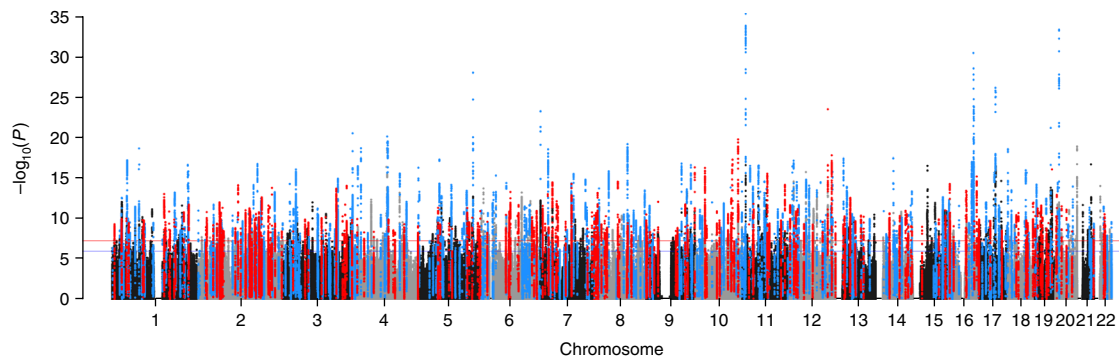


Fig. 2 | Manhattan plot showing the minimum P -value for the association across all blood pressure traits in the discovery stage excluding known and previously reported variants. Discovery genome-wide association meta-analysis in 757,601 individuals excluding variants in 274 known loci. Plot gives the minimum P -value, computed using inverse-variance fixed-effects meta-analysis across SBP, DBP and PP. The y axis shows the $-\log_{10} P$ values and the x-axis shows their chromosomal positions. Horizontal red and blue lines represent the thresholds of $P = 5 \times 10^{-8}$ for genome-wide significance and $P = 1 \times 10^{-6}$ for selecting SNPs for replication, respectively. SNPs in blue are in LD ($r^2 > 0.8$) with the 325 novel variants independently replicated from the two-stage design, whereas SNPs in red are in LD ($r^2 > 0.8$) with 210 SNPs identified through the one-stage design with internal replication. Any loci in black or gray that exceed the significance thresholds were significant in the discovery meta-analysis but did not meet the criteria of replication in the one- or two-stage designs.

types. We found several potential long-range target genes that did not overlap with the sentinel SNPs in the LD block. For example, the *TGFB2* gene forms a 1.2-Mb regulatory loop with SNPs in the *SLC30A10* locus, and the *TGFBRI* promoter forms a 100-kb loop with the *COL15A1* locus (Supplementary Table 8).

Our expression quantitative trait locus (eQTL) analysis identified 60 novel loci with eQTLs in arterial tissue and 20 in adrenal (Supplementary Table 9), substantially increasing those identified in our previously published GWAS on ~ 140 k UKB individuals¹⁰. An example is SNP rs31120122, which defines an aortic eQTL affecting expression of the *MED8* gene within the *SZT2* locus. In combination with Hi-C interaction data in HVMSC, this supports a role for *MED8* in blood pressure regulation, possibly mediated through expression of smooth muscle cell differentiation. Hi-C interactions provide supportive evidence for involvement of a further 36 arterial eGenes (genes whose expression is affected by the eQTLs) that are distal to their eQTLs (for example, *PPHLN1*, *ERAP2*, *FLRT2*, *ACVR2A*, *POU4F1*).

Using DeepSEA, we found 198 SNPs in 121 novel loci with predicted effects on transcription factor binding or on chromatin marks in tissues relevant for blood pressure biology, such as vascular tissue, smooth muscle and the kidney (Supplementary Table 8).

We used our genome-wide data at a false discovery rate (FDR) $< 1\%$ to robustly assess tissue enrichment of blood pressure loci using DEPICT and identified enrichment across 50 tissues and cells (Supplementary Fig. 5a and Supplementary Table 10a). Enrichment was greatest for the cardiovascular system, especially blood vessels ($P = 1.5 \times 10^{-11}$) and the heart ($P = 2.7 \times 10^{-5}$). Enrichment was high in adrenal tissue ($P = 3.7 \times 10^{-4}$), and, for the first time to our knowledge, we observed high enrichment in adipose tissues ($P = 9.8 \times 10^{-9}$) corroborated by eQTL enrichment analysis ($P < 0.05$) (Supplementary Fig. 6 and Supplementary Table 9). Evaluation of enriched mouse knockout phenotype terms also pointed to the importance of vascular morphology ($P = 6 \times 10^{-15}$) and development ($P = 2.1 \times 10^{-18}$) in blood pressure. With addition of our novel blood pressure loci, we identified new findings from both the gene ontology and protein–protein interaction subnetwork enrichments, which highlight the transforming growth factor- β (TGF β) ($P = 2.3 \times 10^{-13}$) and related SMAD pathways ($P = 7 \times 10^{-15}$) (Supplementary Fig. 5b–d and Supplementary Table 10b).

We used FORGE²⁵ to investigate the regulatory regions for cell type specificity from DNase I hypersensitivity sites. This showed

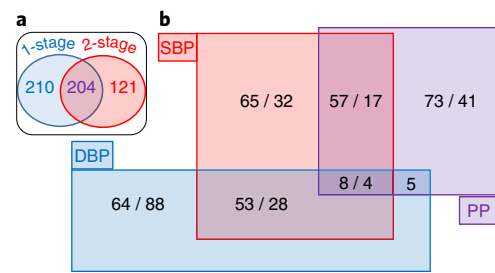


Fig. 3 | Venn diagrams of novel locus results. **a**, Comparison of one-stage and two-stage design analysis criteria. For all 535 novel loci, we compare the results according to the association criteria used for the one-stage and the two-stage design. 210 loci exclusively met the one-stage analysis criteria ($P < 5 \times 10^{-9}$ in the discovery meta-analysis ($n = 757,601$), $P < 0.01$ in UKB ($n = 458,577$), $P < 0.01$ in ICBP ($n = 299,024$) and concordant direction of effect between UKB and ICBP). The P -values for the discovery and the ICBP meta-analyses were calculated using inverse-variance fixed-effects meta-analysis. The P -values in UKB were derived from linear mixed modeling using the software package BOLT-LMM¹⁷. Of the 325 novel replicated loci from the two-stage analysis (genome-wide significance in the combined meta-analysis, $P < 0.01$ in the replication meta-analysis and concordant direction of effect), 204 loci would also have met the one-stage criteria, whereas 121 were identified only by the two-stage analysis. **b**, Overlap of associations across blood pressure traits. For all 535 novel loci, we show the number of loci associated with each blood pressure trait. We present the two-stage loci first, followed by the one-stage loci.

strongest enrichment ($P < 0.001$) in the vasculature and highly vascularized tissues, as reported in previous blood pressure genetic studies¹⁰ (Supplementary Fig. 7).

Potential therapeutic targets. Ingenuity pathway analysis and upstream regulator assessment showed enrichment of canonical pathways implicated in cardiovascular disease, including pathways targeted by antihypertensive drugs (for example, nitric oxide signaling), and also suggested some potential new targets, such as relaxin signaling. Notably, upstream regulator analysis identified several blood pressure therapeutic targets, such as angiotensinogen, calcium channels, progesterone, natriuretic peptide receptor, angiotensin converting enzyme, angiotensin receptors and endothelin receptors (Supplementary Fig. 8).

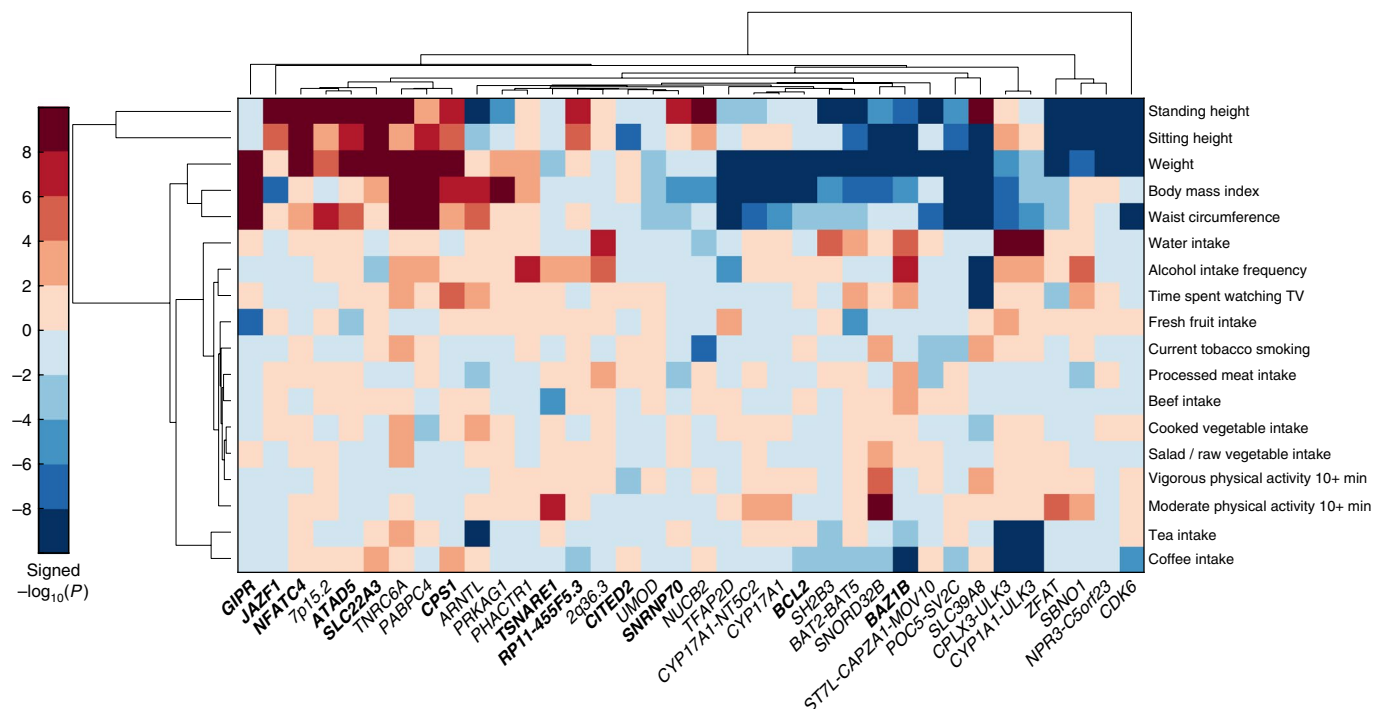


Fig. 4 | Association of blood pressure loci with lifestyle traits. Plot shows unsupervised hierarchical clustering of blood pressure loci based on associations with lifestyle-related factors. For the sentinel SNP at each blood pressure locus (x axis), we calculated the $-\log_{10}(P) \times \text{sign}(\beta)$ (aligned to blood pressure-raising allele) as retrieved from the Gene Atlas catalog. The P -values in Gene Atlas were calculated applying linear mixed models. Blood pressure loci and traits were clustered according to the Euclidean distance among $-\log_{10}(P) \times \text{sign}(\beta)$. Red squares indicate direct associations with the trait of interest and blue squares inverse associations. Only SNPs with at least one association at $P < 1 \times 10^{-6}$ with at least one of the traits examined are annotated in the heat-map. All 901 loci are considered, both known and novel; novel loci are in bold.

We developed a cumulative tally of functional evidence at each variant to assist in variant or gene prioritization at each locus and present a summary of the vascularily expressed genes contained within the 535 novel loci, including a review of their potential drug-gability (Supplementary Fig. 9). The overlap between blood pressure-associated genes and those associated with antihypertensive drug targets further demonstrates new genetic support for known drug mechanisms. For example, we report five novel blood pressure associations with targets of five antihypertensive drug classes (Supplementary Table 11), including the *PKD2L1*, *SLC12A2*, *CACNA1C*, *CACNB4* and *CA7* loci, targeted by potassium-sparing diuretics (amiloride), loop diuretics (bumetanide and furosemide), dihydropyridine, calcium channel blockers, non-dihydropyridines and thiazide-like diuretics (chlortalidone), respectively. Notably, in all but the last case, functional variants in these genes are the best candidates in each locus.

Concordance of blood pressure variants and lifestyle exposures.

We examined association of sentinel SNPs at the 901 blood pressure loci with blood pressure-associated lifestyle traits¹⁴ in UKB using either the Stanford Global Biobank Engine ($n=327,302$) or Gene Atlas ($n=408,455$). With corrected $P < 1 \times 10^{-6}$, we found genetic associations of blood pressure variants with daily fruit intake, urinary sodium and creatinine concentration, body mass index (BMI), weight, waist circumference, and intakes of water, caffeine and tea ($P=1.0 \times 10^{-7}$ to $P=1.3 \times 10^{-46}$). Specifically, SNP rs13107325 in *SLC39A8* is a novel locus for frequency of drinking alcohol ($P=3.5 \times 10^{-15}$) and time spent watching television ($P=2.3 \times 10^{-11}$), as well as being associated with BMI ($P=1.6 \times 10^{-33}$), weight ($P=8.8 \times 10^{-16}$) and waist circumference ($P=4.7 \times 10^{-11}$) (Supplementary Table 12). We used unsupervised hierarchical clustering for the 36 blood pressure loci that showed at

least one association at $P < 1 \times 10^{-6}$ with the lifestyle-related traits in UKB (Fig. 4). The heat map summarizes the locus-specific associations across traits and highlights heterogeneous effects with anthropometric traits across the loci examined. For example, it shows clusters of associations between blood pressure-raising alleles and either increased or decreased adult height and weight. We note that some observed cross-trait associations are in opposite directions to those expected epidemiologically.

Association lookups with other traits and diseases. We further evaluated cross-trait and disease associations using GWAS Catalog²⁶, PhenoScanner²⁷ and DisGeNET^{28,29}. The GWAS Catalog and PhenoScanner search of published GWAS showed that 77 of our 535 novel loci (using sentinel SNPs or proxies with $r^2 \geq 0.8$) are also significantly associated with other traits and diseases (Fig. 5 and Supplementary Table 13). We identified *APOE* as a highly cross-related blood pressure locus showing associations with lipid levels, cardiovascular-related outcomes and Alzheimer's disease, highlighting a common link between cardiovascular risk and cognitive decline (Fig. 5). Other loci overlap with anthropometric traits, including BMI, birth weight and height (Fig. 5), and with DisGeNET terms related to lipid measurements, cardiovascular outcomes and obesity (Fig. 6).

We did lookups of our sentinel SNPs in ¹H NMR lipidomics data on plasma ($n=2,022$) and data from the Metabolon platform ($n=1,941$) in the Airwave Study³⁰, and used PhenoScanner to test SNPs against published significant ($P < 5 \times 10^{-8}$) genome- vs. metabolome-wide associations in plasma and urine (Methods). Ten blood pressure SNPs showed association with lipid particle metabolites and a further 31 SNPs (8 also on PhenoScanner) showed association with metabolites on the Metabolon platform, highlighting lipid pathways, amino acids (glycine, serine and glutamine),

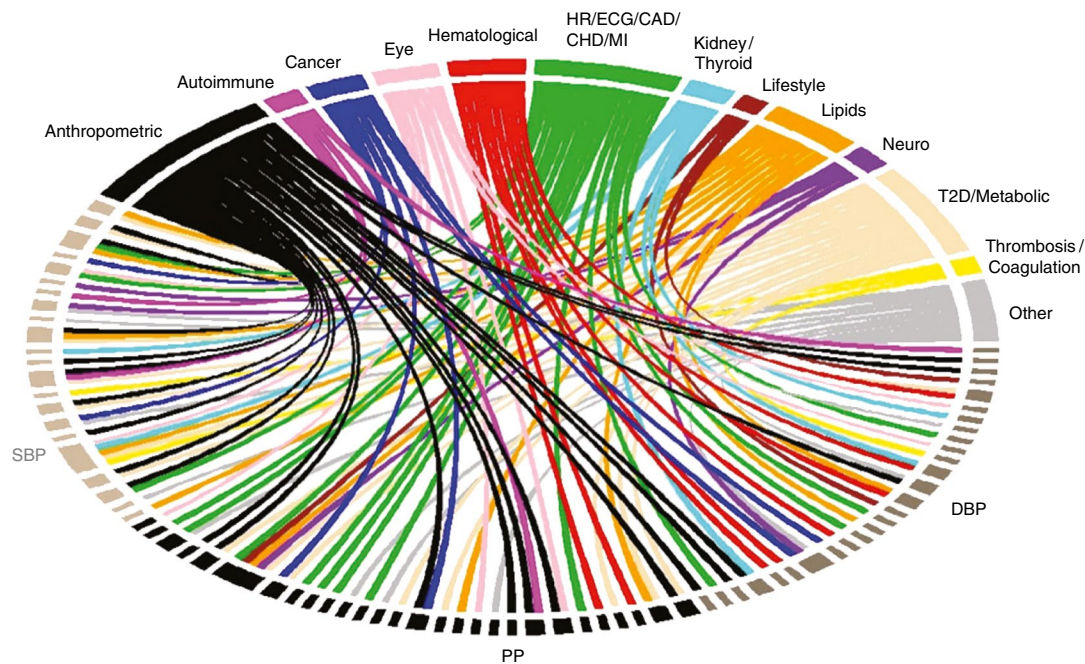


Fig. 5 | Association of blood pressure loci with other traits and diseases. Plot shows results from associations with other traits that were extracted from the GWAS catalog and PhenoScanner databases for the 535 novel sentinel SNPs, including proxies in LD ($r^2 \geq 0.8$) with genome-wide significant associations. HR, heart rate; ECG, electrocardiographic traits; CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction; T2D, type 2 diabetes.

tricarboxylic acid cycle intermediates (succinylcarnitine) and drug metabolites (Supplementary Tables 14 and 15). These findings suggest a close metabolic coupling of blood pressure regulation with lipid and energy metabolism.

Genetic risk of increased blood pressure, hypertension and cardiovascular disease. A weighted GRS for blood pressure across all 901 loci was associated with a 10.4 mm Hg higher, sex-adjusted mean SBP in UKB comparing the top and bottom quintiles of the GRS distribution (95% CI 10.2 to 10.6 mm Hg, $P < 1 \times 10^{-300}$) and with 12.9 mm Hg difference in SBP (95% CI 12.6 to 13.1 mm Hg, $P < 1 \times 10^{-300}$) comparing the top and bottom deciles (Fig. 7a and Supplementary Table 16). In addition, we observed over three-fold sex-adjusted higher risk of hypertension (OR 3.34; 95% CI 3.24 to 3.45; $P < 1 \times 10^{-300}$) between the top and bottom deciles of the GRS in UKB (Fig. 7a). Sensitivity analyses in the independent Airwave cohort gave similar results (Supplementary Table 17). We also found that the GRS was associated with increased, sex-adjusted risk of incident stroke, myocardial infarction and all incident cardiovascular outcomes, comparing top and bottom deciles of the GRS distribution, with odds ratios of 1.47 (95% CI 1.35 to 1.59, $P = 1.1 \times 10^{-20}$), 1.50 (95% CI 1.28 to 1.76, $P = 8.0 \times 10^{-7}$) and 1.52 (95% CI 1.26 to 1.82, $P = 7.7 \times 10^{-6}$), respectively (Fig. 7b and Supplementary Table 16).

Extending analyses to other ancestries. We examined associations with blood pressure of both individual SNPs and the GRS among unrelated individuals of African and South Asian descent in UKB for the 901 known and novel loci. Compared to Europeans, 62.4%, 62.5% and 64.8% of the variants among Africans ($n = 7,782$) and 74.2%, 72.3% and 75% South Asians ($n = 10,323$) had concordant direction of effect for SBP, DBP and PP, respectively (Supplementary Fig. 10 and Supplementary Table 18). Pearson correlation coefficients with effect estimates in Europeans were $r^2 = 0.37$ and 0.78 for Africans and South Asians, respectively (Supplementary Fig. 11). We then applied the European-derived GRS findings to unrelated

Africans ($n = 6,970$) and South Asians ($n = 8,827$). Blood pressure variants in combination were associated with 6.1 mm Hg (95% CI 4.5 to 7.7; $P = 4.9 \times 10^{-14}$) and 7.4 mm Hg (95% CI 6.0 to 8.7; $P = 1.7 \times 10^{-26}$) higher, sex-adjusted mean SBP among Africans and South Asians, respectively, comparing top and bottom quintiles of the GRS distribution (Supplementary Table 19a,b).

Discussion

Our study of over 1 million people offers an important step forward in understanding the genetic architecture of blood pressure. We identified over 1,000 independent signals at 901 loci for blood pressure traits, and the 535 novel loci more than triples the number of blood pressure loci and doubles the percentage variance explained, illustrating the benefits of large-scale biobanks. By explaining 27% of the estimated heritability for blood pressure, we make major inroads into the missing heritability influencing blood pressure in the population³¹. The novel loci open the vista of entirely new biology and highlight gene regions in systems not previously implicated in blood pressure regulation. This is particularly timely as global prevalence of people with SBP over 110–115 mm Hg, above which cardiovascular risk increases in a continuous graded manner, now exceeds 3.5 billion, of whom over 1 billion are within the treatment range^{32,33}.

Our functional analysis highlights the role of the vasculature and associated pathways in the genetics underpinning blood pressure traits. We show a role for several loci in the TGF β pathway, including SMAD family genes and the TGF β gene locus itself. This pathway affects sodium handling in the kidney and ventricular remodeling, while plasma levels of TGF β have recently been correlated with hypertension (Fig. 8)^{34,35}. The activin A receptor type 1C (*ACVR1C*) gene mediates the effects of the TGF β family of signaling molecules. A blood pressure locus contains the bone morphogenetic protein 2 (*BMP2*) gene in the TGF β pathway, which prevents growth suppression in pulmonary arterial smooth muscle cells and is associated with pulmonary hypertension³⁶. Another blood pressure locus includes the Kruppel-like family 14 (*KLF14*) gene of transcription

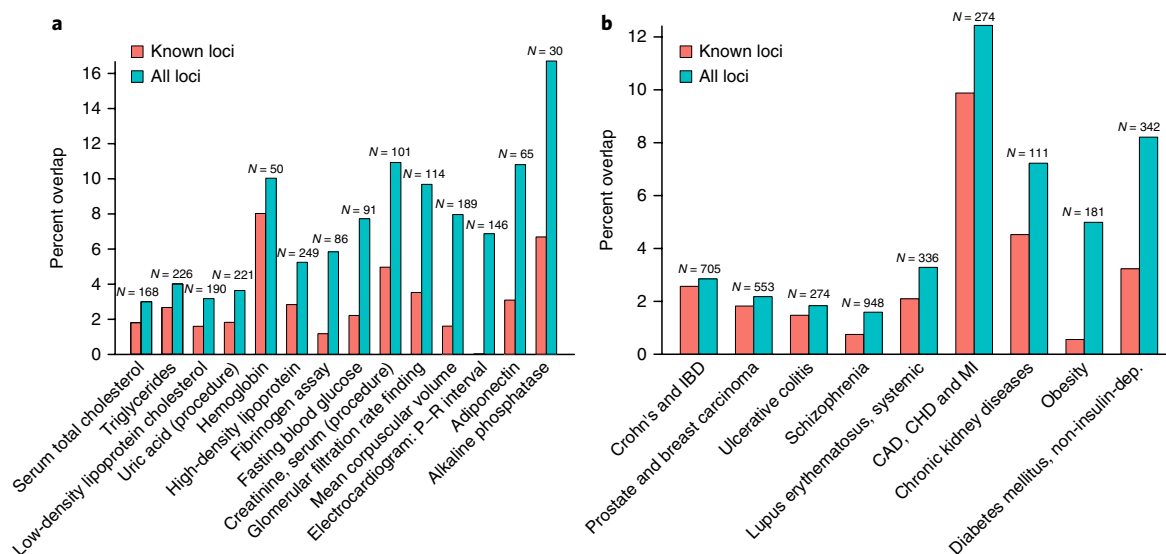


Fig. 6 | Association of blood pressure loci with other traits and diseases. a, b, Plots showing overlap between variants associated to traits (**a**) and diseases (**b**) in the manually curated version of the DisGeNET database, and all variants in LD $r^2 > 0.8$ with the known (red bars) SNPs from the 274 published loci, and all (turquoise bars) blood pressure variants from all 901 loci. Numbers on top of the bars denote the number of SNPs included in DisGeNET for the specific trait or disease. Traits or diseases with an overlap of at least five variants in LD with all markers are shown. The y axis shows the percentage of variants associated with the diseases that is covered by the overlap. For the sake of clarity, the DisGeNET terms for blood pressure and hypertension are not displayed, whereas the following diseases have been combined: coronary artery disease (CAD), coronary heart disease (CHD) and myocardial infarction (MI); prostate and breast carcinoma; Crohn's and inflammatory bowel diseases (IBD).

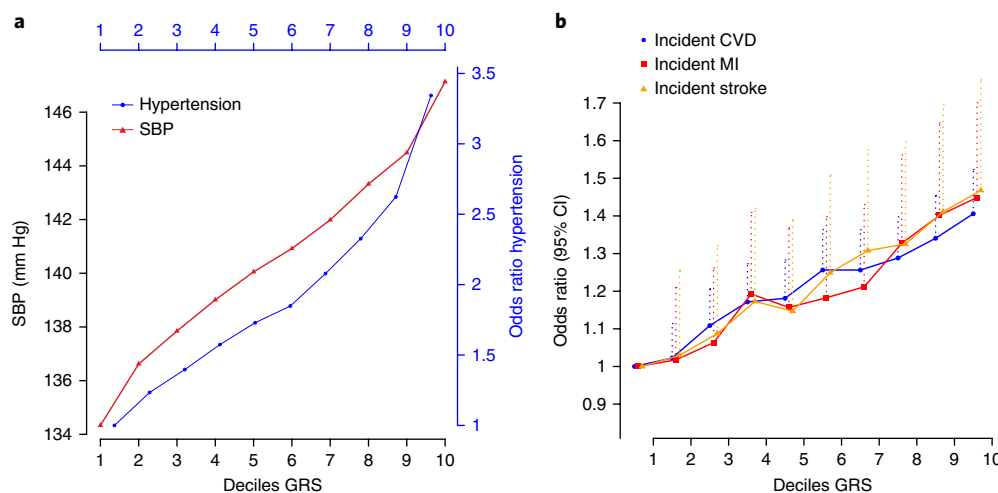


Fig. 7 | Relationship of deciles of the genetic risk score (GRS) based on all 901 loci with blood pressure, risk of hypertension and cardiovascular disease in UKB. a, b, Plots show sex-adjusted mean SBP and odds ratios of hypertension (**a**; $n = 364,520$) and odds ratios of incident cardiovascular disease (CVD), myocardial infarction (MI) and stroke (**b**; $n = 392,092$), comparing each of the upper nine GRS deciles with the lowest decile; dotted lines represent the upper 95% confidence intervals.

factors, which is induced by low levels of TGF β receptor II gene expression and which has also been associated with type 2 diabetes, hypercholesterolemia and atherosclerosis³⁷.

Our analysis shows enrichment of blood pressure gene expression in the adrenal tissue. Autonomous aldosterone production by the adrenal glands is thought to be responsible for 5–10% of all hypertension, rising to ~20% amongst people with resistant hypertension³⁸. Some of our novel loci are linked functionally to aldosterone secretion^{39,40}. For example, the *CTNNB1* locus encodes β -catenin, the central molecule in the canonical Wnt signaling system, required for normal adrenocortical development^{41,42}. Somatic

adrenal mutations of this gene that prevent serine/threonine phosphorylation lead to hypertension through generation of aldosterone-producing adenomas^{43,44}.

Our novel loci also include genes involved in vascular remodeling, such as vascular endothelial growth factor A (*VEGFA*), the product of which induces proliferation, migration of vascular endothelial cells and stimulates angiogenesis. Disruption of this gene in mice resulted in abnormal embryonic blood vessel formation, while allelic variants of this gene have been associated with microvascular complications of diabetes, atherosclerosis and the antihypertensive response to enalapril⁴⁵. We previously reported a

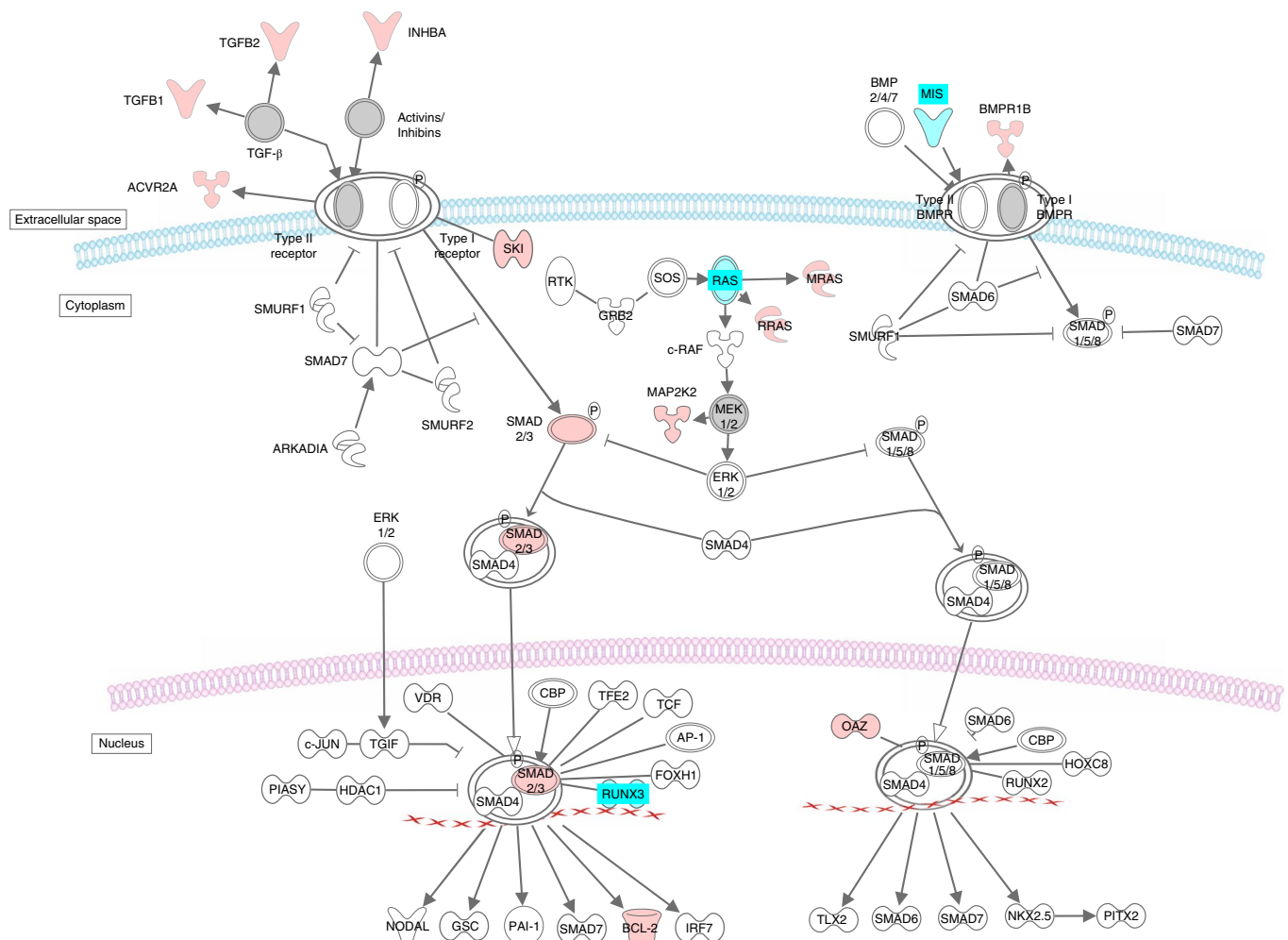


Fig. 8 | Known and novel blood pressure associations in the TGF β signaling pathway. Genes with known associations with blood pressure are indicated in cyan. Genes with novel associations with blood pressure reported in this study are indicated in red. TGF β pathway was derived from an Ingenuity canonical pathway.

fibroblast growth factor (*FGF5*) gene locus in association with blood pressure¹⁰. Here, we additionally identify a new blood pressure locus encoding *FGF9*, which is linked to enhanced angiogenesis and vascular smooth muscle cell differentiation by regulating *VEGFA* expression.

Several of our novel loci contain lipid-related genes, consistent with the observed strong associations among multiple cardio-metabolic traits. For example, the apolipoprotein E gene (*APOE*) encodes the major apoprotein of the chylomicron. Recently, *APOE* serum levels have been correlated with SBP in population-based studies and in murine knockout models; disruption of this gene led to atherosclerosis and hypertension^{46,47}. A second novel blood pressure locus contains the low-density lipoprotein receptor-related protein 4 (*LRP4*) gene, which may be a target for *APOE* and is strongly expressed in the heart in mice and humans. In addition, we identified a novel locus including the apolipoprotein L domain containing 1 gene (*APOLD1*) that is highly expressed in the endothelium of developing tissues (particularly heart) during angiogenesis.

Many of our novel blood pressure loci encode proteins that may modulate vascular tone or signaling. For example, the locus containing urotensin-2 receptor (*UTS2R*) gene encodes a class A rhodopsin family G-protein coupled-receptor that, upon activation by the neuropeptide urotensin II, produces profound vasoconstriction. One novel locus for SBP contains the relaxin gene, encoding a G-protein coupled receptor, with roles in vasorelaxation and cardiac

function; it signals by phosphatidylinositol 3-kinase (PI3K)^{48,49}, an enzyme that inhibits vascular smooth muscle cell proliferation and neo-intimal formation⁵⁰. We identify the *PI3K* gene here as a novel blood pressure locus. We also identify the novel *RAMP2* locus, which encodes an adrenomedullin receptor⁵¹; we previously identified the adrenomedullin (*ADM*) gene as a blood pressure locus¹². Adrenomedullin is known to exert differential effects on blood pressure in the brain (vasopressor) and the vasculature (vasodilator). In addition, a locus containing Rho guanine nucleotide exchange factor 25 (*ARHGEF25*) gene generates a factor that interacts with Rho GTPases involved in contraction of vascular smooth muscle and regulation of responses to angiotensin II⁵².

We evaluated the 901 blood pressure loci for extant or potentially druggable targets. Loci encoding *MARK3*, *PDGFC*, *TRHR*, *ADORA1*, *GABRA2*, *VEGFA* and *PDE3A* are within systems with existing drugs not currently linked to a known antihypertensive mechanism; they may offer repurposing opportunities, for example, detection of *SLC5A1* as the strongest repurposing candidate in a new blood pressure locus targeted by the type 2 diabetes drug canagliflozin. This is important as between 8–12% of patients with hypertension exhibit resistance or intolerance to current therapies and repositioning of a therapy with a known safety profile may reduce development costs.

This study strengthens our previously reported GRS analysis indicating that all blood pressure elevating alleles combined could increase

SBP by 10 mm Hg or more across quintiles or deciles of the population distribution, substantially increasing risk of cardiovascular events¹⁰. We previously suggested that genotyping blood pressure elevating variants in the young could lead to targeted lifestyle intervention in early life that might attenuate the blood pressure rise at older ages¹⁰.

We identified several blood pressure-associated loci that are also associated with lifestyle traits, suggesting shared genetic architecture between blood pressure and lifestyle exposures⁵³. We adjusted our blood pressure GWAS analyses for BMI to control for possible confounding effects, though we acknowledge the potential for collider bias⁵⁴. Nonetheless, our findings of possible genetic overlap between loci associated with blood pressure and lifestyle exposures could support renewed focus on altering specific lifestyle measures known to affect blood pressure⁵⁵.

Despite smaller sample sizes, we observed high concordance with direction of effects on blood pressure traits of blood pressure variants in Africans (>62%) and South Asians (>72%). The GRS analyses show that, in combination, blood pressure variants identified in European analyses are associated with blood pressure in non-European ancestries, though effect sizes were 30–40% smaller.

Our use of a two- and one-stage GWAS design illustrates the value of this approach to minimize the effects of stochastic variation and heterogeneity. The one-stage approach included signals that had independent and concordant support ($P < 0.01$) from both UKB and ICBP, reducing the impact of winners' curse on our findings. Indeed, all but two of the 210 SNPs discovered in the one-stage analysis reach $P < 5 \times 10^{-6}$ in either UKB or ICBP. To further minimize the risk of reporting false positive loci within our one-stage design, we set a stringent overall discovery meta-analysis P -value threshold of $P < 5 \times 10^{-9}$, an order of magnitude smaller than a genome-wide significance P -value, in line with thresholds recommended for whole genome sequencing²². We found high concordance in direction of effects between discovery data in the one-stage approach and the replication resources, with similar distributions of effect sizes for the two approaches. We note that 24 of the one-stage SNPs that reached $P < 5 \times 10^{-9}$ in discovery failed to reach genome-wide significance ($P < 5 \times 10^{-8}$) in the combined meta-analysis of discovery and replication resources, and hence may still require further validation in future, larger studies.

The new discoveries reported here more than triple the number of loci for blood pressure to a total of 901 and represent a substantial advance in understanding the genetic architecture of blood pressure. The identification of many novel genes across the genome could partly support an omnigenic model for complex traits, where genome-wide association of multiple interconnected pathways is observed. However, our strong tissue enrichment shows particular relevance to the biology of blood pressure and cardiovascular disease⁵⁶, suggesting trait-specificity, which could argue against an omnigenic model. Our confirmation of the impact of these variants on blood pressure level and cardiovascular events, coupled with identification of shared risk variants for blood pressure and adverse lifestyle, could contribute to an early life precision medicine strategy for cardiovascular disease prevention.

URLs. FORGE, http://browser.1000genomes.org/Homo_sapiens/UserData/Forge?db=core; Fantom5 data, <http://fantom.gsc.riken.jp/5/>; ENCODE DNase I data, [http://hgdownload.cse.ucsc.edu/goldenPath/hg19/encodeDCC/wgEncodeAwgDnaseMasterSites/\(wgEncodeAwgDnaseMasterSites; accessed using Table browser\);](http://hgdownload.cse.ucsc.edu/goldenPath/hg19/encodeDCC/wgEncodeAwgDnaseMasterSites/(wgEncodeAwgDnaseMasterSites; accessed using Table browser);) ENCODE cell type data, <http://genome.ucsc.edu/ENCODE/cell-Types.html>; GTEx, www.gtexportal.org; DeepSEA, <http://deepsea.princeton.edu/>; WebGestalt, <http://www.webgestalt.org>; IPA, <http://www.qiagen.com/ingenuity>; Mouse Genome Informatics (MGI), <http://www.informatics.jax.org/batch>; Drug Gene Interaction database, <http://www.dgidb.org>; PhenoScanner, <http://www.phenoscanter.medschl.cam.ac.uk> (PhenoScanner integrates results

from the GWAS catalog, <https://www.ebi.ac.uk/gwas/>, and GRASP, <https://grasp.nhlbi.nih.gov/>); DisGeNET, <http://www.disgenet.org>; GeneAtlas, <http://geneatlas.roslin.ed.ac.uk>; Global Biobank Engine, <https://biobankengine.stanford.edu>.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at <https://doi.org/10.1038/s41588-018-0205-x>.

Received: 3 October 2017; Accepted: 9 July 2018;

Published online: 17 September 2018

References

- Forouzanfar, M. H. et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *J. Am. Med. Assoc.* **317**, 165–182 (2017).
- Muñoz, M. et al. Evaluating the contribution of genetics and familial shared environment to common disease using the UK Biobank. *Nat. Genet.* **48**, 980–983 (2016).
- Poulter, N. R., Prabhakaran, D. & Caulfield, M. Hypertension. *Lancet* **386**, 801–812 (2015).
- Feinleib, M. et al. The NHLBI twin study of cardiovascular disease risk factors: methodology and summary of results. *Am. J. Epidemiol.* **106**, 284–285 (1977).
- Cabrera, C. P. et al. Exploring hypertension genome-wide association studies findings and impact on pathophysiology, pathways, and pharmacogenetics. *Wiley Interdiscip. Rev. Syst. Biol. Med.* **7**, 73–90 (2015).
- Ehret, G. B. et al. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat. Genet.* **48**, 1171–1184 (2016).
- Surendran, P. et al. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nat. Genet.* **48**, 1151–1161 (2016).
- Liu, C. et al. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat. Genet.* **48**, 1162–1170 (2016).
- Hoffmann, T. J. et al. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat. Genet.* **49**, 54–64 (2017).
- Warren, H. R. et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat. Genet.* **49**, 403–415 (2017).
- Wain, L. V. et al. Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney. *Hypertension* **70**, e4–e19 (2017).
- Ehret, G. B. et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **478**, 103–109 (2011).
- Sudlow, C. et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).
- Gaziano, J. M. et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J. Clin. Epidemiol.* **70**, 214–223 (2016).
- Leitsalu, L. et al. Cohort profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int. J. Epidemiol.* **44**, 1137–1147 (2015).
- McCarthy, S. et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
- Loh, P. R. et al. Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nat. Genet.* **47**, 284–290 (2015).
- Bulik-Sullivan, B. K. et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
- Ioannidis, J. P., Patsopoulos, N. A. & Evangelou, E. Heterogeneity in meta-analyses of genome-wide association investigations. *PLoS One* **2**, e841 (2007).
- Evangelou, E. & Ioannidis, J. P. Meta-analysis methods for genome-wide association studies and beyond. *Nat. Rev. Genet.* **14**, 379–389 (2013).
- Pulit, S. L., de With, S. A. & de Bakker, P. I. Resetting the bar: statistical significance in whole-genome sequencing-based association studies of global populations. *Genet. Epidemiol.* **41**, 145–151 (2017).
- Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76–82 (2011).

23. Rao, S. S. et al. A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. *Cell* **159**, 1665–1680 (2014).
24. Schmitt, A. D. et al. A compendium of chromatin contact maps reveals spatially active regions in the human genome. *Cell Rep.* **17**, 2042–2059 (2016).
25. Dunham, I. K., Iotchkova, V., Morganella, S. & Birney, E. FORGE: a tool to discover cell specific enrichments of GWAS associated SNPs in regulatory regions. *F1000Res.* **4**, 18 (2015).
26. MacArthur, J. et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res.* **45** D1, D896–D901 (2017).
27. Staley, J. R. et al. PhenoScanner: a database of human genotype-phenotype associations. *Bioinformatics* **32**, 3207–3209 (2016).
28. Piñero, J. et al. DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes. *Database (Oxford)* **2015**, bav028 (2015).
29. Piñero, J. et al. DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. *Nucleic Acids Res.* **45**(D1), D833–D839 (2017).
30. Elliott, P. et al. The Airwave Health Monitoring Study of police officers and staff in Great Britain: rationale, design and methods. *Environ. Res.* **134**, 280–285 (2014).
31. Ehret, G. B. & Caulfield, M. J. Genes for blood pressure: an opportunity to understand hypertension. *Eur. Heart J.* **34**, 951–961 (2013).
32. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* **384**, 591–598 (2014).
33. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1659–1724 (2016).
34. Nakao, E. et al. Elevated plasma transforming growth factor β 1 levels predict the development of hypertension in normotensives: the 14-year follow-up study. *Am. J. Hypertens.* **30**, 808–814 (2017).
35. Feng, W., Dell'Italia, L. J. & Sanders, P. W. Novel paradigms of salt and hypertension. *J. Am. Soc. Nephrol.* **28**, 1362–1369 (2017).
36. Lane, K. B. et al. Heterozygous germline mutations in *BMPR2*, encoding a TGF- β 2 receptor, cause familial primary pulmonary hypertension. *Nat. Genet.* **26**, 81–84 (2000).
37. Voight, B. F. et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat. Genet.* **42**, 579–589 (2010).
38. Douma, S. et al. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. *Lancet* **371**, 1921–1926 (2008).
39. Rossi, G. P. et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J. Am. Coll. Cardiol.* **48**, 2293–2300 (2006).
40. Calhoun, D. A., Nishizaka, M. K., Zaman, M. A., Thakkar, R. B. & Weissmann, P. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* **40**, 892–896 (2002).
41. Drelon, C., Berthon, A., Mathieu, M., Martinez, A. & Val, P. Adrenal cortex tissue homeostasis and zonation: a WNT perspective. *Mol. Cell. Endocrinol.* **408**, 156–164 (2015).
42. El Wakil, A. & Lalli, E. The Wnt/ β -catenin pathway in adrenocortical development and cancer. *Mol. Cell. Endocrinol.* **332**, 32–37 (2011).
43. Teo, A. E. et al. Pregnancy, primary aldosteronism, and adrenal *CTNNB1* mutations. *N. Engl. J. Med.* **373**, 1429–1436 (2015).
44. Tissier, F. et al. Mutations of β -catenin in adrenocortical tumors: activation of the Wnt signaling pathway is a frequent event in both benign and malignant adrenocortical tumors. *Cancer Res.* **65**, 7622–7627 (2005).
45. Oliveira-Paula, G. H. et al. Polymorphisms in *VEGFA* gene affect the antihypertensive responses to enalapril. *Eur. J. Clin. Pharmacol.* **71**, 949–957 (2015).
46. Yang, R. et al. Hypertension and endothelial dysfunction in apolipoprotein E knockout mice. *Arterioscler. Thromb. Vasc. Biol.* **19**, 2762–2768 (1999).
47. Sofat, R. et al. Circulating apolipoprotein E concentration and cardiovascular disease risk: meta-analysis of results from three studies. *PLoS Med.* **13**, e1002146 (2016).
48. Conrad, K. P. Unveiling the vasodilatory actions and mechanisms of relaxin. *Hypertension* **56**, 2–9 (2010).
49. Sun, H. J. et al. Relaxin in paraventricular nucleus contributes to sympathetic override and hypertension via PI3K-Akt pathway. *Neuropharmacology* **103**, 247–256 (2016).
50. Miyamoto, Y. et al. Phosphatidylinositol 3-kinase inhibition induces vasodilator effect of sevoflurane via reduction of Rho kinase activity. *Life Sci.* **177**, 20–26 (2017).
51. Pawlak, J. B., Wetzel-Strong, S. E., Dunn, M. K. & Caron, K. M. Cardiovascular effects of exogenous adrenomedullin and CGRP in Ramp and Calcr1 deficient mice. *Peptides* **88**, 1–7 (2017).
52. Ohtsu, H. et al. Signal-crosstalk between Rho/ROCK and c-Jun NH2-terminal kinase mediates migration of vascular smooth muscle cells stimulated by angiotensin II. *Arterioscler. Thromb. Vasc. Biol.* **25**, 1831–1836 (2005).
53. Tzoulaki, I., Elliott, P., Kontis, V. & Ezzati, M. Worldwide exposures to cardiovascular risk factors and associated health effects: current knowledge and data gaps. *Circulation* **133**, 2314–2333 (2016).
54. Munafò, M. R., Tilling, K., Taylor, A. E., Evans, D. M. & Davey Smith, G. Collider scope: when selection bias can substantially influence observed associations. *Int. J. Epidemiol.* **47**, 226–235 (2018).
55. Pazoki, R. et al. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation* **137**, 653–661 (2018).
56. Boyle, E. A., Li, Y. I. & Pritchard, J. K. An expanded view of complex traits: from polygenic to omnigenic. *Cell* **169**, 1177–1186 (2017).

Acknowledgements

H.R.W. was funded by the National Institute for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Centre at Barts and The London School of Medicine and Dentistry. D.M.-A. is supported by the Medical Research Council (grant number MR/L01632X.1). B.M. holds an MRC eMedLab Medical Bioinformatics Career Development Fellowship, funded from award MR/L016311/1. H.G. was funded by the NIHR Imperial College Health Care NHS Trust and Imperial College London Biomedical Research Centre. C.P.C. was funded by the National Institute for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Centre at Barts and The London School of Medicine and Dentistry. S. Thériault was supported by Canadian Institutes of Health Research; Université Laval (Quebec City, Canada). G.P. was supported by Canada Research Chair in Genetic and Molecular Epidemiology and CISCO Professorship in Integrated Health Biosystems. I. Karaman was supported by the EU PhenoMeNa project (Horizon 2020, 654241). C.P.K. is supported by grant U01DK102163 from the NIH-NIDDK and by resources from the Memphis VA Medical Center. S.D. was supported for this work by grants from the European Research Council (ERC), the EU Joint Programme – Neurodegenerative Disease Research (JPNDR) and the Agence Nationale de la Recherche (ANR). T. Boutin, J. Marten, V.V., A.E.W. and C.H. were supported by a core MRC grant to the MRCHGU QTL in Health and Disease research programme. M. Boehnke is supported by NIH grant R01-DK062370. H.W. and A. Goel acknowledge support of the Tripartite Immunometabolism Consortium (TriC), Novo Nordisk Foundation (grant NNF15CC0018486). N.V. was supported by a Marie Skłodowska-Curie GF grant (661395) and ICIN-NHI. C. Menni is funded by the MRC AimHy (MR/M016560/1) project grant. M.A.N.'s participation is supported by a consulting contract between Data Tecnica International and the National Institute on Aging, NIH. M. Brumat, M. Cocca, I.G., P.G., G.G., A. Morgan, A.R., D.V., C.M.B., C.F.S., M. Taglia and D.T. were supported by Italian Ministry of Health grant RF2010 to P.G. and RC2008 to P.G. D.I.B. is supported by the Royal Netherlands Academy of Science Professor Award (PAH/6635). J.C.C. is supported by the Singapore Ministry of Health's National Medical Research Council under its Singapore Translational Research Investigator (STaR) Award (NMRC/STaR/0028/2017). C.P.C., P.B.M. and M.R.B. were funded by the National Institutes for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Centre at Barts. T.F. is supported by the NIHR Biomedical Research Centre, Oxford. M.R. is the recipient of an award from China Scholarship Council (No. 2011632047). C.L. was supported by the Medical Research Council UK (G1000143, MC_UU_12015/1, MC_PC_13048 and MC_U106179471), Cancer Research UK (C864/A14136) and EU FP6 programme (LSHM_CT_2006_037197). G.B.E. is supported by the Swiss National Foundation SPUM project FN 33CM30-124087, Geneva University, and the Fondation pour Recherches Médicales, Genève. C.M.L. is supported by the Li Ka Shing Foundation; WT-SSI/John Fell funds; the NIHR Biomedical Research Centre, Oxford; Widenlife; and NIH (CRR00070 CR00.01). R.J.E.L. is supported by the NIH (R01DK110113, U01HG007417, R01DK101855 and R01DK107786). D.O.M.-K. is supported by the Dutch Science Organization (ZonMW-VENI Grant 916.14.023). M.M. was supported by the National Institute for Health Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. H.W. and M.F. acknowledge the support of the Wellcome Trust core award (090532/Z/09/Z) and the BHF Centre of Research Excellence (RE/13/1/30181). A. Goel and H.W. acknowledge the European Union Seventh Framework Programme FP7/2007-2013 under grant agreement no. HEALTH-F2-2013-601456 (CVGenes@Target) and A. Goel the Wellcome Trust Institutional strategic support fund. L.R. was supported by Forschungs- und Förder-Stiftung INOVA, Liechtenstein. M. Tomaszewski is supported by British Heart Foundation (PG/17/35/33001). P. Sever is recipient of an NIHR Senior Investigator Award and is supported by the Biomedical Research Centre Award to Imperial College Healthcare NHS Trust. P.v.d.H. was supported by the ICIN-NHI and Marie Skłodowska-Curie GF (call: H2020-MSCA-IF-2014, Project ID: 661395). N.J.W. was supported by the Medical Research Council UK (G1000143, MC_UU_12015/1, MC_PC_13048 and MC_U106179471), Cancer Research UK (C864/A14136) and EU FP6 programme (LSHM_CT_2006_037197). E.Z. was supported by the Wellcome Trust (WT098051). J.N.H. was supported by the Vanderbilt Molecular and Genetic Epidemiology of Cancer (MAGEC) training program, funded by T32CA160056 (PI: X.-O. Shu) and by VA grant 1I01CX000982. A. Giri was supported by VA grant 1I01CX000982. T.L.E. and D.R.V.E. were supported by grant R21HL121429 from NHLBI.

NIH. A.M.H. was supported by VA Award #101BX003360. C.J.O. was supported by VA Boston Healthcare, Section of Cardiology and Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. The MRC/BHF Cardiovascular Epidemiology Unit is supported by the UK Medical Research Council (MR/L003120/1), British Heart Foundation (RG/13/13/30194) and UK National Institute for Health Research Cambridge Biomedical Research Centre. J. Danesh is a British Heart Foundation Professor and NIHR Senior Investigator. L.V.W. holds a GlaxoSmithKline/British Lung Foundation Chair in Respiratory Research. P.E. acknowledges support from the NIHR Biomedical Research Centre at Imperial College Healthcare NHS Trust and Imperial College London, the NIHR Health Protection Research Unit in Health Impact of Environmental Hazards (HPRU-2012-10141), and the Medical Research Council (MRC) and Public Health England (PHE) Centre for Environment and Health (MR/L01341X/1). P.E. is a UK Dementia Research Institute (DRI) professor at Imperial College London, funded by the MRC, Alzheimer's Society and Alzheimer's Research UK. He is also associate director of Health Data Research—UK London, funded by a consortium led by the Medical Research Council. M.J.C. was funded by the National Institute for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Centre at Barts and The London School of Medicine and Dentistry. M.J.C. is a National Institute for Health Research (NIHR) senior investigator, and this work is funded by the MRC eMedLab award to M.J.C. and M.R.B. and by the NIHR Biomedical Research Centre at Barts.

This research has been conducted using the UK Biobank Resource under application numbers 236 and 10035. This research was supported by the British Heart Foundation (grant SP/13/2/30111). Large-scale comprehensive genotyping of UK Biobank for cardiometabolic traits and diseases: UK CardioMetabolic Consortium (UKCMC).

Computing: This work was enabled using the computing resources of (i) the UK Medical Bioinformatics aggregation, integration, visualisation and analysis of large, complex data (UK Med-Bio), which is supported by the Medical Research Council (grant number MR/L01632X/1), and (ii) the MRC eMedLab Medical Bioinformatics Infrastructure, supported by the Medical Research Council (grant number MR/L016311/1). The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services. C.P.K. is an employee of the US Department of Veterans Affairs. Opinions expressed in this paper are those of the authors and do not necessarily represent the opinion of the Department of Veterans Affairs or the United States Government.

Author contributions

Central analysis. E.E., H.R.W., D.M.-A., B.M., R.P., H.G., G.N., N.D., C.P.C., I. Karaman, F.L.N., M.E., K.W., E.T., L.V.W.

Writing of the manuscript. E.E., H.R.W., D.M.-A., B.M., R.P., H.G., I.T., M.R.B., L.V.W., P.E., M.J.C. (with group leads E.E., H.R.W., L.V.W., P.E., M.J.C.). All authors critically reviewed and approved the final version of the manuscript.

ICBP-Discovery contributor. (3C-Dijon) S.D., M.S., P. Amouyel, G.C., C.T.; (AGES-Reykjavik) V. Gudnason, L.J.L., A.V.S., T.B.H.; (ARIC) D.E.A., E.B., A. Chakravarti, A.C.M., P.N.; (ASCOT) N.R.P., D.C.S., A.S., S. Thom, P.B.M., P. Sever, M.J.C., H.R.W.; (ASPS) E.H., Y.S., R. Schmidt, H. Schmidt; (B58C) D.P.S., (BHS) A. James, N. Shrine; (BioMe (formerly IPM)) E.P.B., Y. Lu, R.J.E.L.; (BRIGHT) J.C., M.F., M.J.B., P.B.M., M.J.C., H.R.W.; (CHS) J.C.B., K.R., K.D.T., B.M.P.; (Cilento study) M. Ciullo, T. Nutile, D.R., R. Soric; (COLAUS) M. Bochud, Z.K., P.V.; (CROATIA_Korcula) J. Marten, A.F.W.; (CROATIA_SPLIT) I. Kolcic, O.P., T.Z.; (CROATIA_Vis) J.E.H., I.R., V.V.; (EPIC) K.-T.K., R.J.E.L., N.J.W.; (EPIC-CVD) W.-Y.L., P. Surendran, A.S.B., J. Danesh, J.M.M.H.; (EPIC-Norfolk, Fenland-OMICS, Fenland-GWAS) J.-H.Z.; (EPIC-Norfolk, Fenland-OMICS, Fenland-GWAS, InterAct-GWAS) J.L., C.L., R.A.S., N.J.W.; (ERF) N.A., B.A.O., C.M.v.D.; (Fenland-Exome, EPIC-Norfolk-Exome) S.M.W., F.H.S., S.-J.H., D.L.;

(FINRISK (COROGENE_CTRL)) P.J., K.K., M.P., A.-P.S.; (FINRISK_PREDICT_CVD) A.S.H., A. Palotie, S.R., V.S.; (FUSION) A.U.J., M. Boehnke, F. Collins, J.T., (GAPP) S. Thériault, G.P., D.C., L.R.; (Generation Scotland (GS:SFHS)) T. Boutin, C.H., A. Campbell, S.P.; (GoDARTs) N. Shah, A.S.E.D., A.D.M., C.N.A.P.; (GRAPHIC) P.S.B., C.P.N., N.J.S., M.D.T.; (H2000_CTRL) A. Jula, P.K., S. Koskinen, T. Niiranen; (HABC) Y. Liu, M.A.N., T.B.H.; (HCS) J.R.A., E.G.H., C.O., R.J. Scott; (HTO) K.L.A., H.J.C., B.D.K., M. Tomaszewski, C. Mamasoula; (ICBP-SC) G.A., T.F., M.-R.J., A.D.J., M. Larson, C.N.-C.; (INGI-CARL) I.G., G.G., A. Morgan, A.R.; (INGI-FVG) M. Brumat, M. Cocca, P.G., D.V.; (INGI-VB) C.M.B., C.E.S., D.T., M. Traglia; (JUPITER) F.G., L.M.R., P.M.R., D.I.C.; (KORA S3) C.G., M. Laan, E.O., S.S.; (KORA S4) A. Peters, J.S.R.; (LBC1921) S.E.H., D.C.M.L., A. Pattie, J.M.S.; (LBC1936) G.D., I.J.D., A.J.G., L.M.L.; (Lifelines) N.V., M.H.d.B., M.A.S., P.v.d.H.; (LOLIPOP) J.C.C., J.S.K., B.L., W.Z.; (MDC) P. Almgren, O.M.; (MESA) X.G., W.P., J.I.R., J.Y.; (METSIM) A.U.J., M. Laakso; (MICROS) F.D.G.M., A.A.H., P.P.P.; (MIGEN) R.E., S. Kathiresan, J. Marrugat, D.S.; (NEO) R.L.-G., R.d.M., R.N., D.O.M.-K.; (NESDA) Y.M., I.M.N., B.W.J.H.P., H. Snieder; (NSPHS) S.E., U.G., Å. Johansson; (NTR) D.I.B., E.J.d.G., J.-J.H., G.W.; (ORCADES) H.C., P.K.J., S.H.W., J.F.W.; (PIVUS) L. Lin, C.M.L., J.S., A. Mahajan; (Prevend) N.V., P.v.d.H.; (PROCARDIS) M.F., A. Goel, H.W.; (PROSPER) J. Deelen, J.W.J., D.J.S., S. Trompet; (RS) O.H.F., A. Hofman, A.G.U., G.C.V.; (SardiNIA) J. Ding, Y.Q., F. Cucca, E.G.L.; (SHIP) M.D., R.R., A.T., U.V.; (STR) M. Fränberg, A. Hamsten, R.J. Strawbridge, E.L.; (TRAILS) C.A.H., A.J.O., H.R., P.J.v.d.M.; (TwinsUK) M.M., C. Menni, T.D.S.; (UKHLS) B.P.P., E.Z.; (ULSAM) V. Giedraitis, A.P.M., A. Mahajan, E.I.; (WGHS) F.G., L.M.R., P.M.R., D.I.C.; (YFS) M.K., T.L., L.-P.L., O.T.R.

ICBP analysis. T. Blake, C.Y.D., G.B.E., J.K., L. Lin, P.F.O., P.J.M., Q.T.N., R. Jansen, R. Joehanes, A.M.E., A.V.

Replication study contributor. (MVP) J.N.H., A. Giri, D.R.V.E., Y.V.S., K.C., J.M.G., P.W.F.W., P.S.T., C.P.K., A.M.H., C.J.O., T.L.E.; (EGCUT) T.E., R.M., L.M., A. Metspalu.

Airwave Health Monitoring Study. E.E., H.G., A.-C.V., R.P., I. Karaman, I.T., P.E.

Competing interests

K.W. is a commercial partnerships manager for Genomics England, a UK Government company. M.A.N. consults for Illumina Inc, the Michael J. Fox Foundation and University of California Healthcare, among others. A.S.B. has received grants outside of this work from Merck, Pfizer, Novartis, AstraZeneca, Biogen and Bioerativ and personal fees from Novartis. J. Danesh has the following competing interests: Pfizer Population Research Advisory Panel (grant), AstraZeneca (grant), Wellcome Trust (grant), UK Medical Research Council (grant), Pfizer (grant), Novartis (grant), NHS Blood and Transplant (grant), UK Medical Research Council (grant), British Heart Foundation (grant), UK National Institute of Health Research (grant), European Commission (grant), Merck Sharp and Dohme UK Atherosclerosis (personal fees), Novartis Cardiovascular and Metabolic Advisory Board (personal fees), British Heart Foundation (grant), European Research Council (grant), Merck (grant). B.M.P. serves on the DSMB of a clinical trial funded by Zoll LifeCor and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. M.J.C. is Chief Scientist for Genomics England, a UK Government company.

Additional information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41588-018-0205-x>.

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence and requests for materials should be addressed to P.E. or M.J.C.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Evangelos Evangelou^{1,2,207}, Helen R. Warren^{3,4,207}, David Mosen-Ansorena^{1,207}, Borbala Mifsud^{3,207}, Raha Pazoki^{1,207}, He Gao^{1,5,207}, Georgios Ntritsos^{2,207}, Niki Dimou^{2,207}, Claudia P. Cabrera^{3,4}, Ibrahim Karaman¹, Fu Liang Ng³, Marina Evangelou^{1,6}, Katarzyna Witkowska³, Evan Tzanis³, Jacklyn N. Hellwege⁷, Ayush Giri⁸, Digna R. Velez Edwards⁸, Yan V. Sun^{9,10}, Kelly Cho^{11,12}, J. Michael Gaziano^{11,12}, Peter W. F. Wilson¹³, Philip S. Tsao¹⁴, Csaba P. Kovessy¹⁵, Tonu Esko^{16,17}, Reedik Mägi¹⁶, Lili Milani¹⁶, Peter Almgren¹⁸, Thibaud Boutin¹⁹, Stéphanie Debette^{20,21}, Jun Ding²², Franco Giulianini²³, Elizabeth G. Holliday²⁴, Anne U. Jackson²⁵, Ruifang Li-Gao²⁶, Wei-Yu Lin²⁷, Jian'an Luan²⁸, Massimo Mangino^{29,30}, Christopher Oldmeadow²⁴, Bram Peter Prins³¹, Yong Qian²², Muralidharan Sargurupremraj²¹, Nabi Shah^{32,33}, Praveen Surendran²⁷, Sébastien Thériault^{34,35}, Niek Verweij^{17,36,37}, Sara M. Willems²⁸, Jing-Hua Zhao²⁸, Philippe Amouyel³⁸, John Connell³⁹, Renée de Mutsert²⁶, Alex S. F. Doney³², Martin Farrall^{40,41}, Cristina Menni²⁹, Andrew D. Morris⁴², Raymond Noordam⁴³, Guillaume Paré³⁴, Neil R. Poulter⁴⁴, Denis C. Shields⁴⁵, Alice Stanton⁴⁶, Simon Thom⁴⁷, Gonçalo Abecasis⁴⁸, Najaf Amin⁴⁹, Dan E. Arking⁵⁰, Kristin L. Ayers^{51,52}, Caterina M. Barbieri⁵³, Chiara Batini⁵⁴, Joshua C. Bis⁵⁵, Tineka Blake⁵⁴, Murielle Bochud⁵⁶, Michael Boehnke²⁵, Eric Boerwinkle⁵⁷, Dorret I. Boomsma⁵⁸, Erwin P. Bottinger⁵⁹, Peter S. Braund^{60,61}, Marco Brumat⁶², Archie Campbell^{63,64}, Harry Campbell⁶⁵, Aravinda Chakravarti⁵⁰, John C. Chambers^{1,5,66,67,68}, Ganesh Chauhan⁶⁹, Marina Ciullo^{70,71}, Massimiliano Cocca⁷², Francis Collins⁷³, Heather J. Cordell⁵¹, Gail Davies^{74,75}, Martin H. de Borst⁷⁶, Eco J. de Geus⁵⁸, Ian J. Deary^{74,75}, Joris Deelen⁷⁷, Fabiola Del Greco M.⁷⁸, Cumhuri Yusuf Demirkale⁷⁹, Marcus Dörr^{80,81}, Georg B. Ehret^{50,82}, Roberto Elosua^{83,84}, Stefan Enroth⁸⁵, A. Mesut Erzurumluoglu⁵⁴, Teresa Ferreira^{86,87}, Mattias Frånberg^{88,89,90}, Oscar H. Franco⁹¹, Ilaria Gandin⁶², Paolo Gasparini^{62,72}, Vilmantas Giedraitis⁹², Christian Gieger^{93,94,95}, Giorgia Grotto^{62,72}, Anuj Goel^{40,41}, Alan J. Gow^{74,96}, Vilmundur Gudnason^{97,98}, Xiuqing Guo⁹⁹, Ulf Gyllenstein⁸⁵, Anders Hamsten^{88,89}, Tamara B. Harris¹⁰⁰, Sarah E. Harris^{63,74}, Catharina A. Hartman¹⁰¹, Aki S. Havulinna^{102,103}, Andrew A. Hicks⁷⁸, Edith Hofer^{104,105}, Albert Hofman^{91,106}, Jouke-Jan Hottenga⁵⁸, Jennifer E. Huffman^{19,107,108}, Shih-Jen Hwang^{107,108}, Erik Ingelsson^{109,110}, Alan James^{111,112}, Rick Jansen¹¹³, Marjo-Riitta Jarvelin^{1,5,114,115,116}, Roby Joehanes^{107,117}, Åsa Johansson⁸⁵, Andrew D. Johnson^{107,118}, Peter K. Joshi⁶⁵, Pekka Jousilahti¹⁰², J. Wouter Jukema¹¹⁹, Antti Jula¹⁰², Mika Kähönen^{120,121}, Sekar Kathiresan^{17,36,122}, Bernard D. Keavney^{123,124}, Kay-Tee Khaw¹²⁵, Paul Knekt¹⁰², Joanne Knight¹²⁶, Ivana Kolcic¹²⁷, Jaspal S. Kooner^{5,67,68,128}, Seppo Koskinen¹⁰², Kati Kristiansson¹⁰², Zoltan Kutalik^{56,129}, Maris Laan¹³⁰, Marty Larson¹⁰⁷, Lenore J. Launer¹⁰⁰, Benjamin Lehne¹, Terho Lehtimäki^{131,132}, David C. M. Liewald^{74,75}, Li Lin⁸², Lars Lind¹³³, Cecilia M. Lindgren^{40,87,134}, Yongmei Liu¹³⁵, Ruth J. F. Loos^{28,59,136}, Lorna M. Lopez^{74,137,138}, Yingchang Lu⁵⁹, Leo-Pekka Lyytikäinen^{131,132}, Anubha Mahajan⁴⁰, Chrysovalanto Mamasoula¹³⁹, Jaume Marrugat⁸³, Jonathan Marten¹⁹, Yuri Milaneschi¹⁴⁰, Anna Morgan⁶², Andrew P. Morris^{40,141}, Alanna C. Morrison¹⁴², Peter J. Munson⁷⁹, Mike A. Nalls^{143,144}, Priyanka Nandakumar⁵⁰, Christopher P. Nelson^{60,61}, Teemu Niiranen^{102,145}, Ilja M. Nolte¹⁴⁶, Teresa Nutile⁷⁰, Albertine J. Oldehinkel¹⁴⁷, Ben A. Oostra⁴⁹, Paul F. O'Reilly¹⁴⁸, Elin Org¹⁶, Sandosh Padmanabhan^{64,149}, Walter Palmas¹⁵⁰, Aarno Palotie^{103,151,152}, Alison Pattie⁷⁵, Brenda W. J. H. Penninx¹⁴⁰, Markus Perola^{102,103,153}, Annette Peters^{94,95,154}, Ozren Polasek^{127,155}, Peter P. Pramstaller^{78,156,157}, Quang Tri Nguyen⁷⁹, Olli T. Raitakari^{158,159}, Meixia Ren¹⁶⁰, Rainer Rettig¹⁶¹, Kenneth Rice¹⁶², Paul M. Ridker^{23,163}, Janina S. Ried⁹⁴, Harriëtte Riese¹⁴⁷, Samuli Ripatti^{103,164}, Antonietta Robino⁷², Lynda M. Rose²³, Jerome I. Rotter⁹⁹, Igor Rudan¹⁶⁵, Daniela Ruggiero^{70,71}, Yasaman Saba¹⁶⁶, Cinzia F. Sala⁵³, Veikko Salomaa¹⁰², Nilesh J. Samani^{60,61}, Antti-Pekka Sarin¹⁰³, Reinhold Schmidt¹⁰⁴,

Helena Schmidt¹⁶⁶, Nick Shrine⁵⁴, David Siscovick¹⁶⁷, Albert V. Smith^{97,98}, Harold Snieder¹⁴⁶, Siim Sõber¹³⁰, Rossella Sorice⁷⁰, John M. Starr^{74,168}, David J. Stott¹⁶⁹, David P. Strachan¹⁷⁰, Rona J. Strawbridge^{88,89}, Johan Sundström¹³³, Morris A. Swertz¹⁷¹, Kent D. Taylor⁹⁹, Alexander Teumer^{81,172}, Martin D. Tobin⁵⁴, Maciej Tomaszewski^{123,124}, Daniela Toniolo⁵³, Michela Traglia⁵³, Stella Trompet^{119,173}, Jaakko Tuomilehto^{174,175,176,177}, Christophe Tzourio²¹, André G. Uitterlinden^{91,178}, Ahmad Vaez^{146,179}, Peter J. van der Most¹⁴⁶, Cornelia M. van Duijn⁴⁹, Anne-Claire Vergnaud¹, Germaine C. Verwoert⁹¹, Veronique Vitart¹⁹, Uwe Völker^{81,180}, Peter Vollenweider¹⁸¹, Dragana Vuckovic^{62,182}, Hugh Watkins^{40,41}, Sarah H. Wild¹⁸³, Gonneke Willemsen⁵⁸, James F. Wilson^{19,65}, Alan F. Wright¹⁹, Jie Yao⁹⁹, Tatijana Zemunik¹⁸⁴, Weihua Zhang^{1,67}, John R. Attia²⁴, Adam S. Butterworth^{27,185}, Daniel I. Chasman^{23,163}, David Conen^{186,187}, Francesco Cucca^{188,189}, John Danesh^{27,185}, Caroline Hayward¹⁹, Joanna M. M. Howson²⁷, Markku Laakso¹⁹⁰, Edward G. Lakatta¹⁹¹, Claudia Langenberg²⁸, Olle Melander¹⁸, Dennis O. Mook-Kanamori^{26,192}, Colin N. A. Palmer³², Lorenz Risch^{193,194,195}, Robert A. Scott²⁸, Rodney J. Scott²⁴, Peter Sever¹²⁸, Tim D. Spector²⁹, Pim van der Harst¹⁹⁶, Nicholas J. Wareham²⁸, Eleftheria Zeggini³¹, Daniel Levy^{107,118}, Patricia B. Munroe^{3,4}, Christopher Newton-Cheh^{134,197,198}, Morris J. Brown^{3,4}, Andres Metspalu¹⁶, Adriana M. Hung¹⁹⁹, Christopher J. O'Donnell²⁰⁰, Todd L. Edwards⁷, the Million Veteran Program²⁰¹, Bruce M. Psaty^{202,203}, Ioanna Tzoulaki^{1,2,5,207}, Michael R. Barnes^{3,4,207}, Louise V. Wain^{54,61,207}, Paul Elliott^{1,5,204,205,206,207*} and Mark J. Caulfield^{3,4,207*}

¹Department of Epidemiology and Biostatistics, Imperial College London, London, UK. ²Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece. ³William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK. ⁴National Institute for Health Research, Barts Cardiovascular Biomedical Research Center, Queen Mary University of London, London, UK. ⁵MRC-PHE Centre for Environment and Health, Imperial College London, London, UK. ⁶Department of Mathematics, Imperial College London, London, UK. ⁷Division of Epidemiology, Department of Medicine, Institute for Medicine and Public Health, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Tennessee Valley Healthcare System (626)/Vanderbilt University, Nashville, TN, USA. ⁸Vanderbilt Genetics Institute, Vanderbilt Epidemiology Center, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center; Tennessee Valley Health Systems VA, Nashville, TN, USA. ⁹Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA. ¹⁰Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA. ¹¹Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA. ¹²Division of Aging, Department of Medicine, Brigham and Women's Hospital; Department of Medicine, Harvard Medical School, Boston, MA, USA. ¹³Atlanta VAMC and Emory Clinical Cardiovascular Research Institute, Atlanta, GA, USA. ¹⁴VA Palo Alto Health Care System, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA. ¹⁵Nephrology Section, Memphis VA Medical Center and University of Tennessee Health Science Center, Memphis, TN, USA. ¹⁶Estonian Genome Center, University of Tartu, Tartu, Estonia. ¹⁷Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA. ¹⁸Department Clinical Sciences, Malmö, Lund University, Malmö, Sweden. ¹⁹MRC Human Genetics Unit, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland, UK. ²⁰Department of Neurology, Bordeaux University Hospital, Bordeaux, France. ²¹Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, CHU Bordeaux, Bordeaux, France. ²²Laboratory of Genetics and Genomics, NIA/NIH, Baltimore, MD, USA. ²³Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA. ²⁴Hunter Medical Research Institute and Faculty of Health, University of Newcastle, New Lambton Heights, New South Wales, Australia. ²⁵Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA. ²⁶Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands. ²⁷MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. ²⁸MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK. ²⁹Department of Twin Research and Genetic Epidemiology, Kings College London, London, UK. ³⁰NIHR Biomedical Research Centre at Guy's and St Thomas' Foundation Trust, London, UK. ³¹Wellcome Trust Sanger Institute, Hinxton, UK. ³²Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, UK. ³³Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad, Pakistan. ³⁴Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada. ³⁵Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Québec City, Québec, Canada. ³⁶Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA. ³⁷University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, the Netherlands. ³⁸University of Lille, Inserm, Centre Hosp. Univ. Lille, Institut Pasteur de Lille, UMR1167 – RID-AGE – Risk factors and molecular determinants of aging-related diseases, Epidemiology and Public Health Department, Lille, France. ³⁹University of Dundee, Ninewells Hospital & Medical School, Dundee, UK. ⁴⁰Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. ⁴¹Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, UK. ⁴²Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK. ⁴³Department of Internal Medicine, Section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands. ⁴⁴Imperial Clinical Trials Unit, London, UK. ⁴⁵School of Medicine, University College Dublin, Dublin, Ireland. ⁴⁶Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. ⁴⁷International Centre for Circulatory Health, Imperial College London, London, UK. ⁴⁸Center for Statistical Genetics, Department of Biostatistics, SPH II, Washington Heights, Ann Arbor, MI, USA. ⁴⁹Genetic Epidemiology Unit, Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands. ⁵⁰Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. ⁵¹Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK. ⁵²Sema4, a Mount Sinai venture, Stamford, CT, USA. ⁵³Division of Genetics and Cell Biology, San Raffaele Scientific Institute, Milan, Italy. ⁵⁴Department of Health Sciences, University of Leicester, Leicester, UK. ⁵⁵Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle,

WA, USA. ⁵⁶Institute of Social and Preventive Medicine, University Hospital of Lausanne, Lausanne, Switzerland. ⁵⁷Human Genetics Center, School of Public Health, The University of Texas Health Science Center at Houston and Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA. ⁵⁸Department of Biological Psychology, Vrije Universiteit Amsterdam, EMGO+ Institute, VU University Medical Center, Amsterdam, the Netherlands. ⁵⁹The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁶⁰Department of Cardiovascular Sciences, University of Leicester, Leicester, UK. ⁶¹NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK. ⁶²Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy. ⁶³Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK. ⁶⁴Generation Scotland, Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK. ⁶⁵Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK. ⁶⁶Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. ⁶⁷Department of Cardiology, Ealing Hospital, Middlesex, UK. ⁶⁸Imperial College Healthcare NHS Trust, London, UK. ⁶⁹Centre for Brain Research, Indian Institute of Science, Bangalore, India. ⁷⁰Institute of Genetics and Biophysics "A. Buzzati-Traverso", CNR, Napoli, Italy. ⁷¹IRCCS Neuromed, Pozzilli, Isernia, Italy. ⁷²Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy. ⁷³Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD, USA. ⁷⁴Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. ⁷⁵Department of Psychology, University of Edinburgh, Edinburgh, UK. ⁷⁶Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. ⁷⁷Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, the Netherlands. ⁷⁸Institute for Biomedicine, Eurac Research, Bolzano, Italy – Affiliated Institute of the University of Lübeck, Lübeck, Germany. ⁷⁹Mathematical and Statistical Computing Laboratory, Office of Intramural Research, Center for Information Technology, National Institutes of Health, Bethesda, MD, USA. ⁸⁰Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany. ⁸¹DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, Germany. ⁸²Cardiology, Department of Medicine, Geneva University Hospital, Geneva, Switzerland. ⁸³CIBERCV & Cardiovascular Epidemiology and Genetics, IMIM, Barcelona, Spain. ⁸⁴Faculty of Medicine, Universitat de Vic–Central de Catalunya, Vic, Spain. ⁸⁵Department of Immunology, Genetics and Pathology, Uppsala Universitet, Science for Life Laboratory, Uppsala, Sweden. ⁸⁶Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK. ⁸⁷Big Data Institute, Li Ka Shing Center for Health for Health Information and Discovery, Oxford University, Oxford, UK. ⁸⁸Cardiovascular Medicine Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden. ⁸⁹Centre for Molecular Medicine, L8:03, Karolinska Universitetssjukhuset, Solna, Sweden. ⁹⁰Department of Numerical Analysis and Computer Science, Stockholm University, Stockholm, Sweden. ⁹¹Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands. ⁹²Department of Public Health and Caring Sciences, Geriatrics, Uppsala, Sweden. ⁹³Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. ⁹⁴Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. ⁹⁵German Center for Diabetes Research (DZD e.V.), Neuherberg, Germany. ⁹⁶Department of Psychology, School of Social Sciences, Heriot-Watt University, Edinburgh, UK. ⁹⁷Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ⁹⁸Icelandic Heart Association, Kopavogur, Iceland. ⁹⁹The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, LABioMed at Harbor-UCLA Medical Center, Torrance, CA, USA. ¹⁰⁰Intramural Research Program, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, MD, USA. ¹⁰¹Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. ¹⁰²Department of Public Health Solutions, National Institute for Health and Welfare (THL), Helsinki, Finland. ¹⁰³Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. ¹⁰⁴Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria. ¹⁰⁵Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria. ¹⁰⁶Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. ¹⁰⁷National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA, USA. ¹⁰⁸The Population Science Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA. ¹⁰⁹Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden. ¹¹⁰Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA. ¹¹¹Department of Pulmonary Physiology and Sleep, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, Western Australia, Australia. ¹¹²School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia. ¹¹³Department of Psychiatry, VU University Medical Center, Amsterdam Neuroscience, Amsterdam, the Netherlands. ¹¹⁴Biocenter Oulu, University of Oulu, Oulu, Finland. ¹¹⁵Center For Life-course Health Research, University of Oulu, Oulu, Finland. ¹¹⁶Unit of Primary Care, Oulu University Hospital, Oulu, Oulu, Finland. ¹¹⁷Hebrew SeniorLife, Harvard Medical School, Boston, MA, USA. ¹¹⁸Population Sciences Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA. ¹¹⁹Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. ¹²⁰Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland. ¹²¹Department of Clinical Physiology, Finnish Cardiovascular Research Center – Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland. ¹²²Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, MA, USA. ¹²³Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. ¹²⁴Division of Medicine, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK. ¹²⁵Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, UK. ¹²⁶Data Science Institute and Lancaster Medical School, Lancaster, UK. ¹²⁷Department of Public Health, Faculty of Medicine, University of Split, Split, Croatia. ¹²⁸National Heart and Lung Institute, Imperial College London, London, UK. ¹²⁹Swiss Institute of Bioinformatics, Lausanne, Switzerland. ¹³⁰Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia. ¹³¹Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland. ¹³²Department of Clinical Chemistry, Finnish Cardiovascular Research Center – Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland. ¹³³Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden. ¹³⁴Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. ¹³⁵Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA. ¹³⁶Mindich Child Health Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹³⁷Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland. ¹³⁸University College Dublin, UCD Conway Institute, Centre for Proteome Research, UCD, Belfield, Dublin, Ireland. ¹³⁹Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK. ¹⁴⁰Department of Psychiatry, Amsterdam Public Health and Amsterdam Neuroscience, VU University Medical Center/GGZ inGeest, Amsterdam, the Netherlands. ¹⁴¹Department of Biostatistics, University of Liverpool, Liverpool, UK. ¹⁴²Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA. ¹⁴³Data Tecnica International, Glen Echo, MD, USA. ¹⁴⁴Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA. ¹⁴⁵Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland. ¹⁴⁶Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. ¹⁴⁷Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. ¹⁴⁸SGDP Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ¹⁴⁹British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK. ¹⁵⁰Department of Medicine, Columbia University Medical Center, New York, NY, USA. ¹⁵¹Analytic and Translational Genetics Unit, Department of Medicine, Department of Neurology and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. ¹⁵²The Stanley Center for Psychiatric Research and Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, MA,

USA. ¹⁵³University of Tartu, Tartu, Estonia. ¹⁵⁴German Center for Cardiovascular Disease Research (DZHK), partner site Munich, Neuherberg, Germany. ¹⁵⁵Psychiatric Hospital “Sveti Ivan”, Zagreb, Croatia. ¹⁵⁶Department of Neurology, General Central Hospital, Bolzano, Italy. ¹⁵⁷Department of Neurology, University of Lübeck, Lübeck, Germany. ¹⁵⁸Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland. ¹⁵⁹Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland. ¹⁶⁰Fujian Key Laboratory of Geriatrics, Department of Geriatric Medicine, Fujian Provincial Hospital, Fujian Medical University, Fuzhou, China. ¹⁶¹Institute of Physiology, University Medicine Greifswald, Karlsburg, Germany. ¹⁶²Department of Biostatistics, University of Washington, Seattle, WA, USA. ¹⁶³Harvard Medical School, Boston, MA, USA. ¹⁶⁴Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland. ¹⁶⁵Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK. ¹⁶⁶Gottfried Schatz Research Center for Cell Signaling, Metabolism & Aging, Molecular Biology and Biochemistry, Medical University of Graz, Graz, Austria. ¹⁶⁷The New York Academy of Medicine, New York, NY, USA. ¹⁶⁸Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK. ¹⁶⁹Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, Glasgow, UK. ¹⁷⁰Population Health Research Institute, St George's, University of London, London, UK. ¹⁷¹Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. ¹⁷²Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany. ¹⁷³Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands. ¹⁷⁴Dasman Diabetes Institute, Dasman, Kuwait. ¹⁷⁵Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland. ¹⁷⁶Department of Public Health, University of Helsinki, Helsinki, Finland. ¹⁷⁷Saudi Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia. ¹⁷⁸Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands. ¹⁷⁹Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran. ¹⁸⁰Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany. ¹⁸¹Department of Internal Medicine, University Hospital, CHUV, Lausanne, Switzerland. ¹⁸²Experimental Genetics Division, Sidra Medical and Research Center, Doha, Qatar. ¹⁸³Centre for Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK. ¹⁸⁴Department of Biology, Faculty of Medicine, University of Split, Split, Croatia. ¹⁸⁵The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, UK. ¹⁸⁶Division of Cardiology, University Hospital, Basel, Switzerland. ¹⁸⁷Division of Cardiology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada. ¹⁸⁸Institute of Genetic and Biomedical Research, National Research Council (CNR), Monsezzato, Cagliari, Italy. ¹⁸⁹Department of Biomedical Sciences, University of Sassari, Sassari, Italy. ¹⁹⁰Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland. ¹⁹¹Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. ¹⁹²Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands. ¹⁹³Labormedizinisches Zentrum Dr. Risch, Schaan, Liechtenstein. ¹⁹⁴Private University of the Principality of Liechtenstein, Triesen, Liechtenstein. ¹⁹⁵University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. ¹⁹⁶Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. ¹⁹⁷Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. ¹⁹⁸Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA. ¹⁹⁹Tennessee Valley Healthcare System (Nashville VA) & Vanderbilt University, Nashville, TN, USA. ²⁰⁰VA Boston Healthcare, Section of Cardiology and Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. ²⁰¹A consortium acknowledgement and affiliations for the Million Veteran Program are included in Supplementary Note 2. ²⁰²Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA, USA. ²⁰³Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA. ²⁰⁴National Institute for Health Research Imperial Biomedical Research Centre, Imperial College Healthcare NHS Trust and Imperial College London, London, UK. ²⁰⁵UK Dementia Research Institute (UK DRI) at Imperial College London, London, UK. ²⁰⁶Health Data Research-UK London substantive site, London, UK. ²⁰⁷These authors contributed equally: Evangelos Evangelou, Helen R. Warren, David Mosen-Ansorena, Borbala Mifsud, Raha Pazoki, He Gao, Georgios Ntritsos, Niki Dimou, Ioanna Tzoulaki, Michael R. Barnes, Louise V. Wain, Paul Elliott, Mark J. Caulfield.

*e-mail: p.elliott@imperial.ac.uk; m.j.caulfield@qmul.ac.uk

Methods

UK Biobank (UKB) data. We performed a genome-wide association study (GWAS) analysis in 458,577 UKB participants¹³ (Supplementary Note 1). These consist of 408,951 individuals from UKB genotyped at 825,927 variants with a custom Affymetrix UK Biobank Axiom Array chip and 49,626 individuals genotyped at 807,411 variants with a custom Affymetrix UK BiLEVE Axiom Array chip from the UK BiLEVE study³⁷, which is a subset of UKB. SNPs were imputed centrally by UKB using a reference panel that merged the UK10K and 1000 Genomes Phase 3 panel as well as the Haplotype Reference Consortium (HRC) panel³⁸. For the current analysis, only SNPs imputed from the HRC panel were considered.

UKB phenotypic data. Following quality control (QC) (Supplementary Note 1), we restricted our data to a subset of post-QC individuals of European ancestry combining information from self-reported and genetic data (Supplementary Note 1), resulting in a maximum of $n = 458,577$ individuals (Fig. 1 and Supplementary Fig. 12).

Three blood pressure traits were analyzed: systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP; the difference between SBP and DBP). We calculated the mean SBP and DBP values from two automated ($n = 418,755$) or two manual ($n = 25,888$) blood pressure measurements. For individuals with one manual and one automated blood pressure measurement ($n = 13,521$), we used the mean of these two values. For individuals with only one available blood pressure measurement ($n = 413$), we used this single value. After calculating blood pressure values, we adjusted for medication use by adding 15 and 10 mm Hg to SBP and DBP, respectively, for individuals reported to be taking blood pressure-lowering medication ($n = 94,289$)³⁹. Descriptive summary statistics are shown in Supplementary Table 1a.

UKB analysis models. For the UKB GWAS, we performed linear mixed model (LMM) association testing under an additive genetic model of the three (untransformed) continuous, medication-adjusted blood pressure traits (SBP, DBP, PP) for all measured and imputed genetic variants in dosage format using the BOLT-LMM (v2.3) software¹⁷. We also calculated the estimated SNP-wide heritability (h^2) in our data. Within the association analysis, we adjust for the following covariates: sex, age, BMI and a binary indicator variable for UKB vs. UK BiLEVE to account for the different genotyping chips. The analysis of all HRC-imputed SNPs was restricted to variants with MAF $\geq 1\%$ and INFO > 0.1 .

Genomic inflation and confounding. We applied the univariate LD score regression method (LDSR)¹⁸ to test for genomic inflation (expected for polygenic traits such as blood pressure, with large sample sizes, and especially also from analyses of such dense genetic data with many SNPs in high LD)⁶⁰. LDSR intercepts (and standard errors) were 1.217 (0.018), 1.219 (0.020) and 1.185 (0.017) for SBP, DBP and PP, respectively, and were used to adjust the UKB GWAS results for genomic inflation, before the meta-analysis.

International Consortium for Blood Pressure (ICBP) GWAS. ICBP GWAS is an international consortium to investigate blood pressure genetics⁶. We combined previously reported post-QC GWAS data from 54 studies ($n = 150,134$)^{11,12,61}, with newly available GWAS data from a further 23 independent studies ($n = 148,890$) using a fixed-effects inverse-variance-weighted meta-analysis. The 23 studies providing new data were ASCOT-SC, ASCOT-UK, BRIGHT, Dijon 3C, EPIC-CVD, GAPP, HCS, GS-SFHS, Lifelines, JUPITER, PREVEND, TWINSUK, GWAS-Fenland, InterAct-GWAS, OMICS-EPIC, OMICS-Fenland, UKHLS, GoDARTS-Illumina and GoDarts-Affymetrix, NEO, MDC, Sardinia and METSIM.

All study participants were Europeans and were imputed to either the 1000 Genomes Project Phase 1 integrated release v3 (March 2012) all-ancestry reference panel⁶² or the HRC panel¹⁶. The final enlarged ICBP GWAS dataset included 77 cohorts ($n = 299,024$).

Full study names, cohort information and general study methods are included in Supplementary Tables 1b and 20a–c. Genomic control was applied at the study level. The LDSR intercepts (standard error) for the ICBP GWAS meta-analysis were 1.089 (0.012), 1.086 (0.012) and 1.066 (0.011) for SBP, DBP and PP, respectively.

Meta-analyses of discovery datasets. We performed a fixed-effects inverse-variance-weighted meta-analysis using METAL^{20,63} to obtain summary results from the UKB and ICBP GWAS, for up to $n = 757,601$ participants and ~ 7.1 million SNPs with MAF $\geq 1\%$ for variants present in both the UKB data and ICBP meta-analysis for all three traits. The LDSR intercepts (standard error) in the discovery meta-analysis of UKB and ICBP were 1.156 (0.020), 1.160 (0.021) and 1.113 (0.018) for SBP, DBP and PP, respectively. The LDSR intercept (standard error) after the exclusion of all published blood pressure variants (see below) in the discovery meta-analysis of UKB and ICBP was 1.090 (0.018), 1.097 (0.017) and 1.064 (0.015) for SBP, DBP and PP, respectively, hence showing little inflation in the discovery GWAS after the exclusion of published loci (Supplementary Fig. 13). No further correction was applied to the discovery meta-analysis of UKB and ICBP GWAS.

Previously reported variants. We compiled from the peer-reviewed literature all 357 SNPs previously reported to be associated with blood pressure at the time

that our analysis was completed, that have been identified and validated as the sentinel SNP in primary analyses from previous blood pressure genetic association studies. These 357 published SNPs correspond to 274 distinct loci, according to locus definition of (i) SNPs within ± 500 kb distance of each other and (ii) SNPs in LD, using a threshold of $r^2 \geq 0.1$, calculated with PLINK (v2.0). We then augment this list to all SNPs present within our data, which are contained within these 274 published blood pressure loci; i.e., all SNPs that are located ± 500 kb from each of the 357 published SNPs and/or in LD with any of the 357 previously validated SNPs ($r^2 \geq 0.1$).

Identification of novel signals using two-stage and one-stage study designs.

To identify novel signals of association with blood pressure, two complementary study designs (which we term here “two-stage design” and “one-stage design”) were implemented in order to maximize the available data and minimize reporting of false positive associations.

Overview of two-stage design. All of the following criteria had to be satisfied for a signal to be reported as a novel signal of association with blood pressure using our two-stage design:

1. The sentinel SNP shows significance ($P < 1 \times 10^{-6}$) in the discovery meta-analysis of UKB and ICBP, with concordant direction of effect between UKB and ICBP.
2. The sentinel SNP is genome-wide significant ($P < 5 \times 10^{-8}$) in the combined meta-analysis of discovery and replication (MVP and EGCUT) (replication, described below).
3. The sentinel SNP shows support ($P < 0.01$) in the replication meta-analysis of MVP and EGCUT alone (Supplementary Note 1).
4. The sentinel SNP has concordant direction of effect between the discovery and the replication meta-analyses.
5. The sentinel SNP must not be located within any of the 274 previously reported loci described above.

The primary replicated trait was then defined as the blood pressure trait with the most significant association from the combined meta-analysis of discovery and replication (in the case where a SNP was replicated for more than one blood pressure trait).

Selection of variants from the discovery meta-analysis. We considered for follow-up SNPs in loci non-overlapping with previously reported loci according to both an LD threshold of r^2 of 0.1 and a 1-Mb interval region, as calculated by PLINK⁶⁴. We obtained a list of such SNPs with $P < 1 \times 10^{-6}$ for any of the three blood pressure traits that also had concordant direction of effect between UKB vs. ICBP (Supplementary Table 21). By ranking the SNPs by significance in order of minimum P -value across all blood pressure traits, we performed an iterative algorithm to determine the number of novel signals (Supplementary Note 1) and identify the sentinel (most significant) SNP per locus.

Replication analysis. We considered SNPs with MAF $\geq 1\%$ for independent replication in MVP (max $n = 220,520$)¹⁴ and in EGCUT Biobank ($n = 28,742$)¹⁵ (Supplementary Note 1). This provides a total of $n = 249,262$ independent samples for individuals of European descent available for replication. Additional information on the analyses of the two replication datasets is provided in the Supplementary Note 1 and Supplementary Table 1c. The two datasets were then combined using fixed-effects inverse-variance-weighted meta-analysis, and summary results for all traits were obtained for the replication meta-analysis dataset.

Combined meta-analysis of discovery and replication meta-analyses. The meta-analyses were performed within METAL software⁶³ using fixed-effects inverse-variance-weighted meta-analysis (Supplementary Note 1). The variants from the discovery GWAS that required proxies for replication are shown in Supplementary Table 22. The combined meta-analysis of both the discovery data ($n = 757,601$) and replication meta-analysis (max $n = 249,262$) provided a maximum sample size of $n = 1,006,863$.

Overview of one-stage design. Variants that were looked up but did not replicate according to the two-stage criteria were considered in a one-stage design. All of the following criteria had to be satisfied for a signal to be reported as a novel signal of association with blood pressure using our one-stage criteria:

1. The sentinel SNP has $P < 5 \times 10^{-9}$ in the discovery (UKB + ICBP) meta-analysis.
2. The sentinel SNP shows support ($P < 0.01$) in the UKB GWAS alone.
3. The sentinel SNP shows support ($P < 0.01$) in the ICBP GWAS alone.
4. The sentinel SNP has concordant direction of effect between UKB and ICBP datasets.
5. The sentinel SNP must not be located within any of the 274 previously reported loci described above (Supplementary Table 4) or the recently reported non-replicated loci from Hoffman et al.⁹ (Supplementary Table 23).

We selected the one-stage P -value threshold to be an order of magnitude more stringent than a genome-wide significance P -value so as to ensure robust results

and to minimize false positive findings. The threshold of $P < 5 \times 10^{-9}$ has been proposed as a more conservative statistical significance threshold, for example, for whole-genome sequencing-based studies²¹.

Selection of variants from the meta-analysis of UKB and ICBP was performed as described above for the two-stage design.

Conditional analysis. We performed conditional analyses using the GWAS discovery meta-analysis data in order to identify any independent secondary signals in addition to the sentinel SNPs at the 901 loci. We used two different methodological approaches, each using the genome-wide complex traits analysis (GCTA) software²²: (i) full genome-wide conditional analysis with joint multivariate analysis and stepwise model selection across all three blood pressure traits, and (ii) locus-specific conditional analysis for the primary blood pressure trait conditioning on the sentinel SNPs within each locus (Supplementary Note 1). For robustness, secondary signals are only reported if obtained from both approaches. All secondary signals with $MAF \geq 1\%$ were selected at genome-wide significance level and confirmed to be pairwise-LD-independent ($r^2 < 0.1$), as well as not being in LD with any of the published or sentinel SNPs at any of the 901 blood pressure-associated loci ($r^2 < 0.1$). In all cases, the UKB data was used as the reference genetic data for LD calculation, restricted to individuals of European ancestry only.

Variant-level functional analyses. We used an integrative bioinformatics approach to collate functional annotation at both the variant level (for each sentinel SNP within all blood pressure loci) and the gene level (using SNPs in LD $r^2 \geq 0.8$ with the sentinel SNPs). At the variant level, we use Variant Effect Predictor (VEP) to obtain comprehensive characterization of variants, including consequence (for example, downstream or noncoding transcript exon), information on nearest genomic features and, where applicable, amino acid substitution functional impact, based on SIFT and PolyPhen. The biomaRt R package is used to further annotate the nearest genes.

We evaluated all SNPs in LD ($r^2 \geq 0.8$) with our novel sentinel SNPs for evidence of mediation of expression quantitative trait loci (eQTL) in all 44 tissues using the Genotype-Tissue Expression (GTEx) database, to highlight specific tissue types that show eQTLs for a larger than expected proportion of novel loci. We further sought to identify novel loci with the strongest evidence of eQTL associations in arterial tissue in particular. A locus is annotated with a given eGene only if the most significant eQTL SNP for the given eGene is in high LD ($r^2 \geq 0.8$) with the sentinel SNP, suggesting that the eQTL signal colocalizes with the sentinel SNP.

We annotated nearest genes, eGenes (genes whose expression is affected by eQTLs) and Hi-C interactors with HUVEC, HVMSC and HAEC expression from the Fantom5 project. Genes that had higher than median expression levels in the given cell types were indicated as expressed.

To identify SNPs in the novel loci that have a noncoding functional effect (influence binding of transcription factors or RNA polymerase, or influence DNase hypersensitivity sites or histone modifications), we used DeepSEA, a deep learning algorithm, which learned the binding and modification patterns of ~900 cell-factor combinations⁶⁵. A change of >0.1 in the binding score predicted by DeepSEA for the reference and alternative alleles was used as cut-off to find alleles with noncoding functional effect (Supplementary Note 1).

We identified potential target genes of regulatory SNPs using long-range chromatin interaction (Hi-C) data from HUVECs²³, aorta, adrenal glands, neural progenitors and mesenchymal stem cells, which are tissues and cell types that are considered relevant for regulating blood pressure²⁴. We find the most significant promoter interactions for all potential regulatory SNPs (RegulomeDB score ≤ 5) in LD ($r^2 \geq 0.8$) with our novel sentinel SNPs and published SNPs, and choose the interactors with the SNPs of highest regulatory potential to annotate the loci.

We then performed overall enrichment testing across all loci. First, we used DEPICT⁶⁶ (Data-driven Expression Prioritized Integration for Complex Traits) to identify tissues and cells that are highly expressed at genes within the blood pressure loci (Supplementary Note 1). Second, we used DEPICT to test for enrichment in gene sets associated with biological annotations (manually curated and molecular pathways, phenotype data from mouse knockout studies) (Supplementary Note 1). We report significant enrichments with a false discovery rate < 0.01 . The variants tested were (i) the 357 published blood pressure-associated SNPs at the time of analysis and (ii) a set including all (published and novel) variants (with novel SNPs filtered by highest significance, $P < 1 \times 10^{-12}$).

Furthermore, to investigate cell type specific enrichment within DNase I sites, we used FORGE, which tests for enrichment of SNPs within DNase I sites in 123 cell types from the Epigenomics Roadmap Project and ENCODE²⁵ (Supplementary Note 1). Two analyses were compared (i) using published SNPs only and (ii) using sentinel SNPs at all 901 loci, in order to evaluate the overall tissue specific enrichment of blood pressure-associated variants.

Gene-level functional analyses. At the gene level, we used Ingenuity Pathway Analysis (IPA) software (IPA, QIAGEN Redwood City) to review genes with prior links to blood pressure, based on annotation with the “Disorder of Blood Pressure,” “Endothelial Development” and “Vascular Disease” Medline Subject Heading

(MESH) terms. We used the Mouse Genome Informatics (MGI) tool to identify blood pressure and cardiovascular relevant mouse knockout phenotypes for all genes linked to blood pressure in our study. We also used IPA to identify genes that interact with known targets of antihypertensive drugs. Genes were also evaluated for evidence of small molecule druggability or known drugs based on queries of the Drug Gene Interaction database.

Lookups in non-European ancestries. As a secondary analysis, we looked up all known and novel blood pressure-associated SNPs in Africans ($n = 7,782$) and South Asians ($n = 10,322$) from UKB using BOLT-LMM analysis for each blood pressure trait within each ancestry (Supplementary Note 1).

Effects on other traits and diseases. We queried SNPs against GWAS catalog²⁶ and PhenoScanner²⁷, including genetics and metabolomics databases, to investigate cross-trait effects, extracting all association results with genome-wide significance at $P < 5 \times 10^{-8}$ for all SNPs in high LD ($r^2 \geq 0.8$) with the 535 sentinel novel SNPs, to highlight the loci with strongest evidence of association with other traits. We further evaluated these effects using DisGeNET^{28,29}. At the gene level, we carried out over-representation enrichment analysis with WebGestalt⁶⁷ on the nearest genes to all blood pressure loci. Moreover, we tested sentinel SNPs at all published and novel ($n = 901$) loci for association with lifestyle-related data including food, water and alcohol intake; anthropomorphic traits; and urinary sodium, potassium and creatinine excretion using the recently developed Stanford Global Biobank Engine and the Gene Atlas⁶⁸. Both are search engines for GWAS findings for multiple phenotypes in UKB. We deemed a locus significant at a Bonferroni-corrected threshold of $P < 1 \times 10^{-6}$.

Genetic risk scores and percentage of variance explained. We calculated a weighted genetic risk score (GRS) (Supplementary Table 24) to provide an estimate of the combined effect of the blood pressure-raising variants on blood pressure and risk of hypertension and applied this to the UKB data (Supplementary Note 1). Our analysis included 423,713 unrelated individuals of European ancestry, of whom 392,092 individuals were free of cardiovascular events at baseline.

We assessed the association of the continuous GRS variable on blood pressure and with the risk of hypertension, with and without adjustment for sex. We then compared blood pressure levels and risk of hypertension, respectively, for individuals in the top vs. bottom quintiles of the GRS distribution. Similar analyses were performed for the top vs. bottom deciles of the GRS distribution. All analyses were restricted to the 392,092 unrelated individuals of European ancestry from UKB. As a sensitivity analysis to assess for evidence of bias in the UKB results, we also carried out similar analyses in Airwave, an independent cohort of $n = 14,004$ unrelated participants of European descent³⁰ (Supplementary Note 1).

We calculated the association of the GRS with cardiovascular disease in unrelated participants in UKB data on the basis of self-reported medical history and linkage to hospitalization and mortality data (Supplementary Table 25). We use logistic regression with binary outcome variables for composite incident cardiovascular disease (Supplementary Note 1), incident myocardial infarction and incident stroke (using the algorithmic UKB definitions) and GRS as explanatory variable (with and without sex adjustment).

We also assessed the association of this GRS with blood pressure in unrelated Africans ($n = 6,970$) and South Asians ($n = 8,827$) from the UKB to see whether blood pressure-associated SNPs identified from GWAS predominantly in Europeans are also associated with blood pressure in populations of non-European ancestry.

We calculated the percentage of variance in blood pressure explained by genetic variants using the independent Airwave cohort ($n = 14,004$) (Supplementary Note 1). We considered three different levels of the GRS: (i) all pairwise-independent, LD-filtered ($r^2 < 0.1$) published SNPs within the known loci; (ii) all known SNPs and sentinel SNPs at novel loci; and (iii) all independent signals at all 901 known and novel loci including the 163 secondary SNPs.

Ethics statement. The UKB study has approval from the North West Multi-Centre Research Ethics Committee. Any participants from UKB who withdrew consent have been removed from our analysis. Each cohort within the ICBP meta-analysis, as well as our independent replication cohorts of MVP and ECGUT, had ethical approval locally. More information on the participating cohorts is available in the Supplementary Note 2.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The genetic and phenotypic UKB data are available upon application to the UK Biobank (<https://www.ukbiobank.ac.uk>). ICBP summary data can be accessed through request to the ICBP steering committee. Contact the corresponding authors to apply for access to the data. The UKB + ICBP summary GWAS discovery data can be accessed by request to the corresponding authors and will be available via LDHub (<http://ldsc.broadinstitute.org/ldhub/>). All replication data generated during this study are included in the published article. For example, association

results of look-up variants from our replication analyses and the subsequent combined meta-analyses are contained within the Supplementary Tables.

References

57. Wain, L. V. et al. Novel insights into the genetics of smoking behaviour, lung function, and chronic obstructive pulmonary disease (UK BiLEVE): a genetic association study in UK Biobank. *Lancet Respir. Med.* **3**, 769–781 (2015).
58. Bycroft, C.F. et al. Genome-wide genetic data on 500,000 UK Biobank participants. Preprint at *bioRxiv* <https://doi.org/10.1101/166298> (2017).
59. Tobin, M. D., Sheehan, N. A., Scurrah, K. J. & Burton, P. R. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat. Med.* **24**, 2911–2935 (2005).
60. Marouli, E. et al. Rare and low-frequency coding variants alter human adult height. *Nature* **542**, 186–190 (2017).
61. Wain, L. V. et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nat. Genet.* **43**, 1005–1011 (2011).
62. 1000 Genomes Project Consortium et al. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
63. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).
64. Purcell, S. et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
65. Zhou, J. & Troyanskaya, O. G. Predicting effects of noncoding variants with deep learning-based sequence model. *Nat. Methods* **12**, 931–934 (2015).
66. Pers, T. H. et al. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6**, 5890 (2015).
67. Wang, J., Vasaike, S., Shi, Z., Greer, M. & Zhang, B. WebGestalt 2017: a more comprehensive, powerful, flexible and interactive gene set enrichment analysis toolkit. *Nucleic Acids Res.* **45**, W130–W137 (2017).
68. Canela-Xandri, O., Rawlik, K. & Tenesa, A. An atlas of genetic associations in UK Biobank. Preprint at *bioRxiv* <https://doi.org/10.1101/176834> (2017).

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see [Reporting Life Sciences Research](#). For further information on Nature Research policies, including our [data availability policy](#), see [Authors & Referees](#) and the [Editorial Policy Checklist](#).

► Experimental design

1. Sample size

Describe how sample size was determined.

Of the total ~500,000 subjects from UK Biobank, we analysed 458,577 subjects which passed QC of the genetic data, were of European ancestry, and met our phenotypic data QC requirements for availability of blood pressure data and covariates.

To maximize sample size in the discovery, we recruited an additional 148,890 samples from 23 new cohorts, in addition to the 150,134 samples already existing from the 54 cohorts within the published ICBP-1000G project, giving a total sample size of 299,024 in the ICBP meta-analysis.

Hence a total discovery sample size of $N=757,601$.

Our combined meta-analysis sample size was $N=1,006,863$ after combining with the data from the replication cohorts ($N=220,520$ from MVP and $N=28,742$ from EGCUT).

2. Data exclusions

Describe any data exclusions.

Within UK Biobank, we excluded samples according to both genetic data quality control (QC) and phenotypic data QC. From genetic data QC, we excluded 968 subjects listed as QC outliers for heterozygosity or missingness within the centrally provided UK Biobank sample QC files, and 378 individuals with sex discordance between the phenotypic and genetically inferred sex. We also restricted to subjects of European ancestry, according to both self-reported ethnicity status and ancestry clustering using PCA data. For phenotypic QC, we excluded any subjects with no BP measurements, missing BMI covariate data, pregnant ($N=372$) and those individuals who had withdrawn consent ($N=36$).

Similar sample QC was performed at study level within each of the ICBP and replication cohorts.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Novel loci identified from our 2-stage approach were robustly replicated using independent replication datasets. Novel loci identified from our 1-stage approach met our criteria for internal replication by showing significant support within each of the UKB and ICBP GWAS datasets separately.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

N/A for GWAS

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

N/A for GWAS
(Note data collection of UK Biobank was done centrally, not performed by us)

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- ☐ ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☒ ☐ A statement indicating how many times each experiment was replicated
- ☐ ☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- ☐ ☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- ☐ ☒ The test results (e.g. P values) given as exact values whenever possible and with confidence intervals noted
- ☐ ☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- ☒ ☐ Clearly defined error bars

See the web collection on [statistics for biologists](#) for further resources and guidance.

► Software

Policy information about [availability of computer code](#)

7. Software

Describe the software used to analyze the data in this study.

For the Primary GWAS analysis, BOLT-LMM software v2.3 was used for running an association analysis using linear mixed modelling; then METAL software was used for all meta-analyses with a fixed effects inverse variance weighted meta-analysis approach.

We used R software for any general statistical analyses, for secondary analyses (e.g. variance explained analyses, risk score analyses) and for producing plots in the figures.

We used PLINK software for LD calculations of variants.

For the bioinformatics analyses, specific software was used for each different analysis. Each method and the software used is described in the Online Methods, the Supplementary Methods and also summarised in Supplementary Figure 3. For example, the Variant Effect Predictor (VEP) tool is used for variant annotation; DEPICT software is used for enrichment testing, etc.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* [guidance for providing algorithms and software for publication](#) provides further information on this topic.

► Materials and reagents

Policy information about [availability of materials](#)

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

N/A (not labwork)

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

N/A

10. Eukaryotic cell lines

- State the source of each eukaryotic cell line used.
- Describe the method of cell line authentication used.
- Report whether the cell lines were tested for mycoplasma contamination.
- If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by [ICLAC](#), provide a scientific rationale for their use.

N/A

N/A

N/A

N/A

► Animals and human research participants

Policy information about [studies involving animals](#); when reporting animal research, follow the [ARRIVE guidelines](#)

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

N/A

Policy information about [studies involving human research participants](#)

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Summary descriptives of UKB, ICBP and MVP/EGCUT individuals are provided in Sup Tables 1a, 1b and 1c, respectively, showing: blood pressure measurements as the phenotype; age, sex and BMI values as covariates; hypertension status and the use of BP-lowering medication.